

# Estimating Cardiovascular Risk in Spain Using Different Algorithms

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**Introduction and objectives.** Although its incidence is low, cardiovascular disease is the most common cause of morbidity and mortality in Spain. A number of different algorithms can be used to calculate cardiovascular disease risk for primary prevention, but their ability to identify patients who will experience a cardiovascular event is not well understood. The objective of this study was to compare the results of using the original Framingham algorithm and two adaptations for low-risk countries: the REGICOR (Registre Gironí del COR) and SCORE (Systematic COronary Risk Evaluation) algorithms.

**Methods.** All cardiovascular events during 5-year follow-up in a cohort of patients without coronary disease in nine autonomous Spanish regions were recorded. The levels of different cardiovascular risk factors were measured between 1995 and 1998. Participants were considered high-risk if their 10-year risk was  $\geq 20\%$  with the Framingham algorithm,  $\geq 10\%$ ,  $\geq 15\%$  or  $\geq 20\%$  with REGICOR, and  $\geq 5\%$  with SCORE.

**Results.** In total, 180 (3.1%) coronary events (112 in men and 68 in women) occurred among the 5732 (57.3% female) participants during follow-up. Of these, 43 died from

cerebrovascular disease, and 24 had a non-coronary vascular event. The REGICOR algorithm had the highest positive predictive value for coronary and cardiovascular disease in all age groups. Moreover, with a 10-year risk limit of 10%, it classified less of the population aged 35-74 years as high-risk (i.e., 12.4%) than the Framingham algorithm (i.e., 22.4%). The SCORE and Framingham algorithms classified 8.4% and 16.6% of the population aged 35-64 years, respectively, as having a high cardiovascular disease risk; with REGICOR, the figure was 7.5%.

**Conclusions.** The REGICOR adapted algorithm was the best predictor of cardiovascular events and classified a smaller proportion of the Spanish population aged 35-74 years as high risk than alternative algorithms.

**Key words:** *Coronary disease. Risk factors. Hypercholesterolemia. Cardiovascular risk.*

SEE EDITORIAL ON PAGES 690-2

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This study received unconditional financial support from Grupo Esteve. It was also part-financed by the Fondo de Investigación Sanitaria research network: Redes Temáticas RECAVA (FIS C03/01), RCESP (FIS C03/09), REDIAPP-Catalunya (FISG03/170), and HERACLES (FIS G03/045), and by the Spanish Ministry of Health and Consumer Affairs, the Instituto de Salud Carlos III, (Red HERACLES RD06/0009).

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Received August 10, 2006.

Accepted for publication April 3, 2007.

## Rendimiento de la estimación del riesgo cardiovascular en España mediante la utilización de distintas funciones

**Introducción y objetivos.** A pesar de que presentan una baja incidencia, las enfermedades cardiovasculares son la causa más frecuente de morbimortalidad en España. Se dispone de diversas funciones para calcular el riesgo cardiovascular en la prevención primaria, cuya capacidad para identificar a los pacientes que desarrollarán acontecimientos cardiovasculares es poco conocida. Comparamos el rendimiento de las funciones de Framingham original, adaptada de REGICOR (Registre Gironí del COR) y SCORE (Systematic COronary Risk Evaluation) para países de bajo riesgo.

**Métodos.** Se registraron todos los acontecimientos cardiovasculares en un seguimiento de 5 años de una cohorte sin enfermedad coronaria en 9 comunidades autónomas. Se midieron los factores de riesgo cardiovascular entre 1995 y 1998. Se consideró que el riesgo era elevado a los 10 años en  $\geq 20\%$  para Framingham,  $\geq 10\%$ ,  $\geq 15\%$  y  $\geq 20\%$  para REGICOR y  $\geq 5\%$  para SCORE.

**Resultados.** Se produjeron 180 (3,1%) acontecimientos coronarios (112 en varones y 68 en mujeres) en las 5.732 personas (57,3% de mujeres) en las que se realizó el seguimiento. Se produjo muerte cerebrovascular en 43 personas, así como 24 acontecimientos vasculares no coronarios. Con la función REGICOR se obtuvo el mayor valor predictivo positivo para enfermedad coronaria y cardiovascular a cualquier edad, y, tomando un límite de 10% de riesgo a los 10 años, se clasificó a menos población de alto riesgo de 35-74 años (12,4%) que con la función de Framingham (22,4%). SCORE y Framingham clasificaron al 8,4 y al 16,6% de la población de 35-64 años como de alto riesgo cardiovascular y REGICOR, al 7,5%.

**Conclusiones.** La función adaptada de REGICOR es la opción aplicable hasta los 74 años que muestra el mejor equilibrio en la capacidad de clasificación de riesgo de acontecimientos cardiovasculares. Su aplicación permite la clasificación de alto riesgo a individuos con un perfil más adecuado para ser candidatos a tratamiento hipolipemiante.

**Palabras clave:** *Enfermedad coronaria. Factores de riesgo. Hipercolesterolemia. Riesgo cardiovascular.*

#### ABBREVIATIONS

IHD: ischemic heart disease  
CVD: cardiovascular disease  
HDL-C: high-density lipoprotein cholesterol  
REGICOR: Girona heart register (REGistre Gironí del COR)  
SCORE: Systematic COronary Risk Evaluation  
VERIFICA: validation of the adapted Framingham individual coronary incident risk algorithm (Validez de la Ecuación del Riesgo Individual de Framingham de Incidentes Coronarios Adaptada)

## INTRODUCTION

Cardiovascular disease (CVD), especially ischemic heart disease (IHD), is one of the most frequent causes of death in Spain.<sup>1</sup> The high level of fatality is similar to that in other industrialized countries.<sup>2,3</sup> However, the incidence of CVD in general and of IHD in particular is among the lowest in the world.<sup>4</sup>

The Framingham algorithms have proved extremely useful tools for screening patients and in primary prevention in countries with a high incidence of coronary and cardiovascular disease.<sup>5</sup> However, they overestimate the risk of coronary heart disease to a greater or lesser extent in several countries.<sup>6-10</sup> The Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice recommends using the Systematic COronary Risk Evaluation (SCORE)

algorithm, and suggests cardiovascular prevention guidelines are adapted to the national population characteristics of the country of use.<sup>11</sup>

One part of the suggested adaptation includes function of risk. A validated methodology to adapt the Framingham algorithm to the reality of each country has been developed and this means we can reliably predict coronary events with precision.<sup>12</sup> The REGICOR (REGistre Gironí del COR) group used this method to adapt the algorithm to population-based data on the prevalence of risk factors and rate of coronary events observed in Spain.<sup>10,13,14</sup> The VERIFICA study (Validation of the adapted Framingham individual coronary incident risk algorithm) demonstrated the reliability and precision of the REGICOR adaptation in Spain.<sup>15</sup>

The range of cardiovascular risk algorithms available means we need to compare their operational performance (sensitivity, specificity, and predictive values) and the percentages of the population classified as high-risk in order to select the most suitable algorithm for clinical practice in Spain.

We compare the performance of the original Framingham algorithm<sup>16</sup> and the REGICOR and SCORE<sup>17</sup> adaptations<sup>13</sup> for countries with low CVD risk, in terms of their ability to classify patients; ie, sensitivity, specificity, and predictive values. We also evaluate the distinctive characteristics of patients considered high-risk by the different algorithms and the percentage of the population classified as high-risk.

## METHODS

### Design

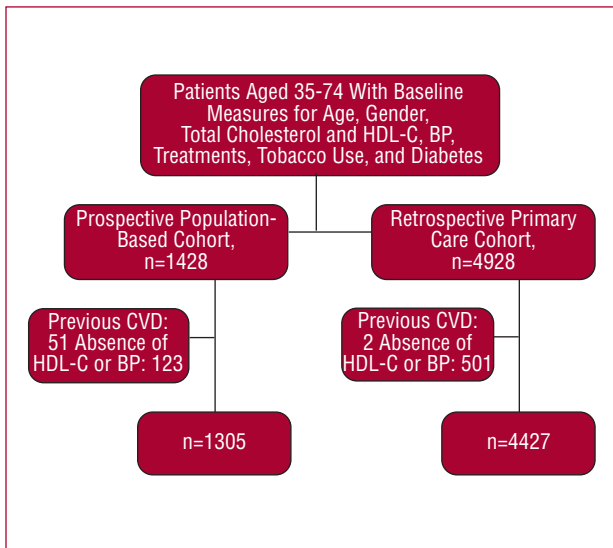
This cohort study enrolled 5732 participants aged 35-74 (Figure 1): 4427 were retrospectively selected at random in 67 health centers in the autonomous Spanish regions of Andalusia, Aragón, Catalonia, the Basque country, Extremadura, Galicia, Balearic Islands, Madrid, and Navarre, from patients for whom baseline data were available (1996-1998); 1305 came from a selected, representative, population-based cohort (1995) with prospective follow-up.<sup>18</sup>

All patients were initially free of IHD, stroke, or peripheral arterial disease and contributed reliable data from January 1995 thru December 1998 on blood pressure (BP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), tobacco use, and diabetes.

We only included patients if we had guaranteed access to information about their condition at the end of the follow-up period (5 years) and were able to conduct further follow-up.

### Sample Size

The number of coronary events recorded at 5 years in the VERIFICA study (n=180) enables us to estimate the



**Figure.** Flowchart on participant enrolment in the combined cohorts. HDL-C indicates high-density lipoprotein cholesterol; CVD, cardiovascular disease; BP, blood pressure.

sensitivity of the tests with 95% confidence interval (CI) (7)%, assuming sensitivity was 40%. Specificity can be estimated with CI 95% lower than (2)%, assuming this was around 80%, given that 5552 patients experienced no coronary events.<sup>15</sup>

## Measurements

In the population-based cohort, all cardiovascular risk factors were measured according to standard procedures.<sup>18</sup> We considered patients to have diabetes when it was previously diagnosed, they were receiving treatment for diabetes, or had glycemia >125 mg/dL on initial examination. We considered patients hypertensive when it was previously diagnosed, they were receiving antihypertensive treatment, or they presented systolic blood pressure (SBP)  $\geq 140$  mm Hg, or diastolic blood pressure (DBP)  $\geq 90$  mm Hg on initial examination. Patients consuming at least 1 cigarette/day during the previous year were considered as smokers. At 5 years, we conducted a telephone follow-up using a structured questionnaire to determine the appearance of events of interest, and patients underwent an electrocardiogram. Moreover, we reviewed primary care and in-hospital clinical records of participants hospitalized during the follow-up.

All primary care cohort participants contributed reliable data on BP, total cholesterol, HDL-C, tobacco use, diabetes, and drug regimens administered in the 5 years prior to inclusion. To establish the follow-up start date and, therefore, the date of risk factor baseline values, we used the date when total cholesterol was

measured. If data on BP or lipids included more than 1 measurement, we calculated the mean as follows: we noted the mean of the first 2 consecutive measurements of total cholesterol and HDL-C in the earliest 3-month period or the earliest isolated measurement from January 1996 thru December 1998. If total cholesterol had been measured alone and total cholesterol and HDL-C later, we recorded the mean of the 2 total cholesterol measurements and the HDL-C value at the second measurement. We recorded BP values measured closest to the date of the cholesterol means used as follows: the mean of the 2 or 3 consecutive measures in the 6 months closest to the date of the first measurement of cholesterol, described above, or the closest value if we had no access to consecutive values over 6 months. We assumed all patients following drug regimens had received the corresponding dietary advice.<sup>15</sup> The family physician was put in contact with all patients during data collection to determine the precise nature of their situation and determine whether they had experienced CVD that had did not appear in clinical records.

For the Framingham and REGICOR algorithms, we evaluated fatal and non-fatal coronary events (including initial angina pectoris); and for the SCORE algorithm, fatal cardiovascular events (coronary events, strokes, heart failure, and peripheral arterial disease). Diagnosis of events of interest was by standard criteria.<sup>15</sup>

## Quality Control of Information

We randomly sampled 15% of patients selected for 3 independent monitors (previously trained physicians) to verify data gathered from the corresponding clinical records. Concordance was very good.<sup>15</sup>

## Follow-Up

We present data from the follow-up conducted during 2003, censored at 5 years.

## Events of Interest

We considered as events of interest the appearance of angina pectoris of any type with electrocardiogram (ECG) changes during pain, exercise test with or without isotopes, or positive coronary angiography, non-fatal, symptomatic, acute myocardial infarction, non-fatal stroke, death from CVD, including congestive heart failure, and other causes of death.

## Ethical Issues

The study was approved by the ethics committees of the Fundaci3n Jordi Gol i Gurina and Barcelona's Instituto Municipal de Asistencia Sanitaria.

**TABLE 1. Characteristics of the Population Studied, Overall and by Gender\***

	Overall (n=5732)	Women (n=3285)	Men (n=2447)
Age, mean (SD), y	56.3 (10.5)	56.8 (10.4)	55.7 (10.6)
Diabetes	16.4%	14.6%	18.8%
SBP, mean (SD), mm Hg	135 (18)	135 (19)	135 (18)
DBP, mean (SD), mm Hg	81 (11)	81 (11)	82 (10)
BP (categories), mm Hg			
Optimal: SBP <120 and DBP <80	13.2%	14.2%	11.7%
Normal: SBP 120-129 or DBP 80-84	17.4%	16.7%	18.3%
Normal-high: SBP 130-139 or DBP 85-89	22.2%	20.6%	24.3%
Level I: SBP 140-159 or DBP 90-99	33.6%	34.7%	32.1%
Levels II-III: SBP=160 or DBP=100	13.6%	3.7%	13.5%
Prior diagnosis of hypertension	44.8%	47.2%	41.7%
Drug treatment for hypertension	30.9%	33.8%	27.3%
Total cholesterol, mean (SD), mg/dL	232 (42)	234 (42)	229 (41)
Total cholesterol categories, mg/dL			
<160	3.8%	3.3%	4.4%
160-199	18.4%	17.4%	19.6%
200-239	35.9%	35.1%	37.1%
240-279	30.1%	30.8%	29.2%
≥280	11.8%	13.4%	9.7%
HDL-C, mean (SD), mg/dL	54 (15)	58 (14)	49 (14)
HDL-C categories, mg/dL			
<35	6.4%	2.9%	11.2%
35-44	21.8%	13.7%	32.7%
45-49	15.6%	15.4%	16.0%
50-59	25.6%	27.8%	22.6%
≥60	30.6%	40.3%	17.6%
Drug treatment for hypercholesterolemia	11.5%	12.1%	10.6%
Smokers or ex-smokers <1 year	24.7%	10.6%	43.8%
Pathologic antecedents: CVD	1.7%	1.3%	2.2%
Heart failure	1.2%	1.2%	1.1%
Peripheral vascular disease	1.1%	0.5%	1.8%
Valvular disease	1.6%	1.4%	1.8%
Observed events at 5 years according to Kaplan-Meier survival curve, %	3.2	1.7	4.0
Number of coronary events in follow-up			
Fatal myocardial infarction	16	9	7
Myocardial infarction	47	11	36
Angina	117	48	69
Coronary events of any kind	180	68	112

\*HDL-C indicates high-density lipoprotein cholesterol; CVD, cerebral vascular disease; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

## Statistical Analysis

We calculated 5-year risk for each patient using 3 equations: the original Framingham<sup>16</sup> algorithm and REGICOR<sup>13</sup> and SCORE<sup>17</sup> algorithms adapted for low-risk countries. We used Kaplan-Meier survival tables to calculate rate of events censored at 5 years.

The algorithm design enabled us to estimate risk in the population aged 35-74 with the original Framingham and adapted REGICOR algorithms, and in the population aged 35-65 with SCORE.

For the original Framingham algorithm, we used a 10-year risk limit of 20% to determine high risk. With

REGICOR, we used 10%, 15%, and 20% limits; with SCORE, we used the recommended 5% limit. For patients <60 years who did not reach the 5% limit, we also calculated SCORE extrapolated to age 60, as recommended in European guidelines.<sup>11</sup> We calculated 5-year rates of incidence of IHD and CVD. We present 95% CI.

We conducted a descriptive study of the cohort and data are expressed as mean (SD) for quantitative variables and as percentages for categorical variables. In comparisons between 2 groups, for presence of events or for classification as high-risk, we used Student *t* test and  $\chi^2$ , respectively.



**TABLE 2. Comparison of Characteristics of Patients With Ischemic Heart Disease and Without it During the 5-Year Follow-Up\***

	Without IHD in Follow-Up (n=5552)	With MI or Angina in Follow-Up (n=180)	P
Age, mean (SD), y	56.2 (10.5)	62.0 (8.8)	<.001
Men	42.1%	62.2%	<.001
High blood pressure levels I-III	46.8%	60.6%	<.001
SBP, mean (SD), mm Hg	135 (18)	141 (18)	<.001
DBP, mean (SD), mm Hg	81 (11)	83 (9)	.052
Total cholesterol, mean (SD), mg/dL	232 (42)	233 (42)	.625
HDL-C <45 mg/dL	27.6%	46.1%	<.001
HDL-C, mean (SD), mg/dL	54 (15)	47 (12)	<.001
Smokers (or ex smokers <1 year)	24.3%	38.9%	<.001
Diabetes	16.0%	30.0%	<.001
Prior diagnosis of high blood pressure	44.2%	64.8%	<.001
Prior treatment for high blood pressure	30.56%	42.25%	.001
Prior treatment for hypercholesterolemia	11.3%	16.7%	.028

\*HDL-C indicates high-density lipoprotein cholesterol; SIHD, symptomatic ischemic heart disease; MI, myocardial infarction; DBP, diastolic blood pressure; SBP, systolic blood pressure.

A *P* value less than .05 was considered significant. Analysis was with S-Plus 2000 (Insightful Corporation, Seattle, WA, U.S.A.) and SAS 8.2 (SAS Institute, Cary, NC, U.S.A.).

## RESULTS

Of 5732 patients enrolled, 3285 were women (57.3%). Table 1 describes characteristics of the sample by gender.

Concordance between data collected and data recorded by monitors was high: demographic data and risk factors,  $\kappa=0.75$ ; events recorded during follow-up,  $\kappa=0.84$ . Intra-class correlation coefficient for continuous variables (age, total cholesterol, HDL-C, SBP, and DBP) was  $\geq 0.90$  in all cases.

During the 5-year follow-up, 180 patients presented IHD episodes (3.1%; 95% CI, 2.7%-9.7%): 112 men and 68 women; and 43 patients (0.75%; 95% CI, 0.53%-0.97%) died from CVD, 25 (1.0%) men, and 18 (0.5%) women. Patients aged 65-74 experienced 46.6% of all cardiovascular events recorded, and 69.8% of fatal events. Moreover, we observed, 24 (0.4%; 95% CI, 0.2-0.6) noncoronary cardiovascular events and 107 (1.9%; 95% CI, 1.5-2.2) deaths from noncardiovascular causes.

Table 2 shows the differences between participants according to appearance of IHD episodes. Among patients presenting IHD, we found a greater percentage of men and a higher prevalence of the risk factors studied, except mean DBP and total cholesterol, with differences between groups. Despite finding no significant differences between groups in mean total cholesterol, we did find differences in HDL-C values, which were lower in patients with IHD. Table 3 shows differences between patients who died from CVD and the rest. Variables with significant

differences were the same as those found for coronary heart disease, except the percentage of smokers and of patients receiving treatment for hypercholesterolemia, which are similar in both groups.

Table 4 describes sensitivity, specificity, and positive predictive value for the 3 algorithms, and the percentage of population classified as high-risk by each of them, with different risk limits for REGICOR. Sensitivity and specificity for predicting coronary, and cardiovascular events were similar for all the algorithms. REGICOR, with 10% and 15% limits, had the highest positive predictive value for both types of event.

Table 5 compares distinctive characteristics of patients classified as high-risk by the 3 algorithms. REGICOR identified greater percentages of women and of patients with HDL-C <45 mg/dL. Extrapolated SCORE and Framingham classified a lower percentage of patients with diabetes in the high-risk group.

Table 6 compares patients aged 35-64 classified with disquieting high-risk by REGICOR and SCORE. Patients classified as high-risk by REGICOR but not by SCORE, presented higher total cholesterol and lower HDL-C than those classified as high-risk by SCORE and not REGICOR.

## DISCUSSION

Our study shows that more than half of the coronary events occur in patients who do not classify as high-risk according to these algorithms. The sensitivity of all the algorithms and limits studied is low (<60%) when detecting patients with IHD in the 5-year follow-up. Depending on the algorithm and limits used, percentages of patients, and characteristics of possible candidates for lipid-lowering drug treatment vary considerably. The percentage of the population aged

**TABLE 3. Comparison of Characteristics of Patients Who Died of Cardiovascular Diseases (Myocardial Infarction, Stroke, or Other) and the Rest of the Sample\***

	Without Cardiovascular Death (n=5689)	With Cardiovascular Death (n=43)	P
Age, mean (SD), y	56.3 (10.5)	65.3 (8.7)	<.001
Men	42.6%	58.1%	.040
High blood pressure levels I-III	47.1%	67.4%	.008
SBP, mean (SD), mm Hg	135 (18)	147 (20)	<.001
DBP, mean (SD), mm Hg	81 (11)	83 (11)	.251
Total cholesterol, mean (SD), mg/dL	232 (42)	223 (37)	.162
HDL-C <45 mg/dL	28.0%	51.2%	.001
HDL-C, mean (SD), mg/dL	54 (15)	47 (13)	.002
Smokers (or ex smokers <1 year)	24.7%	25.6%	.898
Diabetes	16.2%	39.5%	<.001
Prior diagnosis of high blood pressure	44.6%	81.0%	<.001
Prior treatment for high blood pressure	30.8%	55.8%	<.001
Prior treatment for hypercholesterolemia	13.5%	12.8%	.896

\*HDL-C indicates high-density lipoprotein cholesterol; SIHD, symptomatic ischemic heart disease; MI, myocardial infarction; DBP, diastolic blood pressure; SBP, systolic blood pressure.

35-74 selected was 0.8%-22.4%, depending on the algorithm. A balance between sensitivity and specificity in the screening tests is required to select candidates for pharmacologic intervention while avoiding unnecessary treatment. Treatments available produce a relative reduction in risk limited to approximately 30%.<sup>14</sup> In this context, the REGICOR algorithm, with a 10-year risk limit of 10%, can be used in the oldest age groups and provides a good balance between sensitivity, specificity, and positive predictive value. Moreover, it classifies as high-risk a reasonable proportion of the population. As clinical practice

guidelines indicate,<sup>19</sup> in the population it is applicable to, the extrapolated SCORE algorithm classifies the same percentage of patients as high-risk as the original Framingham algorithm does. Both algorithms overestimate the number of events observed in the Spanish population in a similar way.<sup>15,20</sup>

It is fundamental to adapt risk algorithms in countries like Spain where incidence of coronary heart disease is low.<sup>11,15,17</sup> In these countries, most of the population is at a very low level of risk, although this is never absent. Consequently, most cardiovascular events will occur in the low-risk population.

**TABLE 4. Sensitivity, Specificity, and Positive Predictive Value of the Different Tables and Risk Limits for Ischemic Heart Disease and Cardiovascular Disease\***

	Ischemic Heart Disease (n=180)			Cardiovascular Disease (n=247)			High-Risk Population, %
	Sensitivity, %	Specificity, %	PPV, %	Sensitivity, %	Specificity, %	PPV, %	
				35-74 years			
Framingham 20%	57.3	78.5	6.9	53.4	78.9	10.0	22.4
REGICOR 20%	4.9	98.2	6.9	4.0	98.2	8.8	1.9
REGICOR 15%	16.4	95.4	8.9	15.2	95.5	13.0	4.9
REGICOR 10%	36.8	88.3	8.0	32.8	88.5	11.1	12.4
SCORE 5%				Not applicable			
				35-64 years			
Framingham 20%	59.2	84.2	6.7	53.4	84.5	9.6	16.6
REGICOR 20%	5.7	99.3	13.7	3.6	99.3	13.7	0.8
REGICOR 15%	17.4	97.9	14.0	13.5	98.0	17.1	2.4
REGICOR 10%	33.8	93.0	8.5	29.4	93.2	11.7	7.5
SCORE 5%	33.9	92.1	7.7	32.7	92.4	11.7	8.4
SCORE extrapolated 5%	51.5	84.2	5.9	48.6	84.5	8.8	16.5

\*REGICOR indicates REGistre Gironí del COR; SCORE, Systematic COronary Risk Evaluation (not for use with patients aged >64 years); SCORE extrapolated, in patients <60 years with <5% risk at 10 years we also calculated SCORE extrapolated in patients aged 60 years; PPV, positive predictive value.

**TABLE 5. Comparison of Characteristics of Patients <65 Years With High-Risk at 10 Years According to the 3 Algorithms\***

	Framingham ≤20% (n=698)	REGICOR ≥10% (n=315)	SCORE ≥5% (n=352)	SCORE Extrapolated ≥5% (n=693)
Age, mean (SD), y	57.3 (5.3)	58.8 (4.2)	60.9 (2.8)	54.8 (7.6)
Men	74.6%	65.1%	73.9%	78.4%
High blood pressure levels I-III	72.3%	80.3%	79.0%	74.9%
SBP, mean (SD), mm Hg	145 (17)	148 (17)	150 (17)	148 (17)
DBP, mean (SD), mm Hg	86 (10)	87 (10)	86 (10.2)	87 (10)
Total cholesterol, mean (SD), mg/dL	248 (40)	251 (41)	244 (42)	247 (41)
HDL-C <45 mg/dL	62.2%	71.4%	41.2%	44.2%
HDL-C, mean (SD), mg/dL	43 (10)	41 (8)	49 (13)	49 (14)
Smokers (or ex smokers <1 year)	53.2%	58.4%	55.4%	63.5%
Diabetes	45.4%	61%	60.2%	50.9%
Diagnosis of high blood pressure	60.0%	67.8%	67.0%	60.0%
Treatment for high blood pressure	39.9%	46.9%	46.6%	39.8%
Treatment for hypercholesterolemia	22.0%	22.8%	20.2%	18.5%
Coronary events	7.9%	10.2%	8.5%	7.1%
Cardiovascular events	11.2%	13.7%	12.8%	10.5%

\*HDL-C indicates high-density lipoprotein cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure; REGICOR, Registre Gironí del COR; SCORE, Systematic COronary Risk Evaluation; SCORE extrapolated, to patients <60 years with <5% risk at 10 years, we also calculated SCORE extrapolated to patients aged 60 years.

By comparison with patients who presented no coronary event, those who did, initially presented more cardiovascular risk factors, including a lower concentration of HDL-C, but not higher total cholesterol values. This coincides with data reported elsewhere.<sup>21,22</sup> Consequently, it seems important that the algorithm used to calculate risk in Spain should consider the concentration of HDL-C.

Whether patients with diabetes and without IHD present coronary risk similar to that of patients with previous

IHD<sup>19,23</sup> remains controversial. Coronary risk in patients with diabetes but without coronary heart disease is approximately half that of patients without diabetes who present previous IHD.<sup>24,25</sup> Unarguably, diabetes is a cardiovascular risk factor that algorithms must take into account. The Framingham original and REGICOR algorithms include diabetes, whereas SCORE does not differentiate these patients.

**TABLE 6. Comparison of Characteristics of Patients With Disquieting High-Risk Estimated by REGICOR (Registre Gironí del COR) and SCORE (Systematic COronary Risk Evaluation) Risk Algorithms for Low-Risk Countries (Age, 35-64 Years)\***

	REGICOR ≥10% and SCORE <5% (n=104)	REGICOR <10% and SCORE ≥5% (n=141)	P
Age, mean (SD), y	55.4 (4.3)	61.5 (2.3)	<.001
Men	38.5%	67.4%	<.001
High blood pressure levels I-III	81.7%	78.0%	.476
SBP, mean (SD), mm Hg	145 (16)	150 (17)	.011
DBP, mean (SD), mm Hg	89 (10)	86 (10)	.049
Total cholesterol, mg/dL	255 (42)	237 (43)	.001
HDL-C <45 mg/dL	87.5%	7.8%	<.001
HDL-C, mean (SD), mg/dL	38 (6)	60 (13)	<.001
Smokers (or ex smokers <1 year)	41.3%	38.3%	.630
Diabetes	54.8%	54.6%	.975
Coronary events	10.6%	6.4%	.236
Cardiovascular events	11.5%	9.9%	.686

\*HDL-C indicates high-density lipoprotein cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure; REGICOR, Registre Gironí del COR; SCORE, Systematic COronary Risk Evaluation.

Study) and Framingham original, is the only algorithm that does not present significant differences between patients observed and expectations.<sup>26</sup> Risk associated with diabetes should probably include time of evolution as well as the presence of complications like albuminuria.

The different equations do not agree on all patients classified as at-risk. The principal difference in the factors susceptible to modification in the population rests in the greater number of patients with abnormal cholesterol (high total cholesterol and/or low HDL-C) among those only classified as at-risk by REGICOR versus those only classified as at-risk by SCORE.

### Characteristics and Limitations of the Study

Although it is not representative of the population of each of the autonomous Spanish regions, the sample contains participants from the most populous areas of Spain and the sample size was large enough to obtain conclusive results.

Follow-up of the retrospective part of our cohort could imply some bias in information that we attempted to minimize by selecting in health centers with reliable clinical record systems. Our inclusion criteria required that data on patient health status be available via personal or telephone contact and that verification of supposed cardiovascular events and cause of death, if necessary, should be communicated by patients or their families if it was not included in clinical records.

The retrospective cohort consisted of a patient population presenting a greater prevalence of cardiovascular risk factors than that found in the general population. This prevents us from calculating population-based incidence of the disease. Our study design was not intended to obtain a representative sample of the population, as validating a risk algorithm requires a representative sample of each risk category.

One inevitable limitation of contemporary cohort studies is that we cannot avoid the intervention (pharmacologic or not) during the follow-up that may modify risk factors in the participants. The population studied that experienced a coronary event more frequently received hypertensive and hypercholesterolemia treatment at the start of the follow-up in 1995. In contrast, we did not detect differences in prior hypercholesterolemia treatment among patients with and without fatal cardiovascular events. However, adjustment for treatment in the models did not affect results.<sup>15</sup>

### Clinical Implications

Primary prevention of CVD has been controversial.<sup>27-33</sup> Choice of the most adequate algorithm for each country should be based on scientific tests and adapted to

preventative needs and policies.<sup>11</sup> In Spain, the REGICOR algorithm has been adapted to the characteristics of the population, validated for that population<sup>15</sup> and can be applied in those aged 65-74, who experience almost half of all cardiovascular events, and more than two-thirds of fatal cardiovascular events. REGICOR enables us separately to analyze risk in patients with diabetes and provides a better predictive capacity to evaluate patients with abnormal cholesterol.<sup>13,14</sup>

To understand the usefulness of cardiovascular risk algorithms we have to distinguish between diagnostic tests of disease and screening tests. Cardiovascular risk is not a disease to be treated but a way to rationalize the selection of patients to formulate the best possible primary prevention interventions. An algorithm enables us to estimate risk on a population-based scale that implies a high degree of uncertainty when projected on an individual scale; hence, the poor sensitivity of the algorithms. A diagnostic test with 50% sensitivity would not be acceptable to determine whether a patient had myocardial infarction on arriving with chest pain at the Emergency room. For a screening test intended to provide an instrument that helps structure primary cardiovascular prevention, the importance of this characteristic is only relative. Prevention thru advising on lifestyle is universal and practically independent of degree of cardiovascular risk; and the result of estimating risk almost exclusively affects the decision on drug treatment for dyslipidemia. However, no intervention study has selected patients on the basis of coronary or cardiovascular risk. To achieve 100% sensitivity to detect those patients who will experience a cardiovascular event at 10 years we should treat the whole population, and not even then would we manage to avoid all events as preventative efficacy is limited. Table 4 presents data indicating that a 3% improvement in sensitivity in the REGICOR equation would lead to an approximately 1% deterioration in specificity in patients aged 35-74. With the incidence of events observed this implies that each unit of sensitivity is equivalent to 1.8 individuals who will experience a coronary event, and each 1% of specificity is equivalent to some 55 patients who will not. A simple calculation indicates that for each individual aged 35-74 with a future coronary or cardiovascular event in general identified by a risk algorithm, the reduction in specificity implies that approximately 10 patients, who will not experience an event, will receive preventative treatment. In the population aged 35-64, the ratio would be approximately 1:5. This data should enable us to determine how far we can prudently go in our efforts at prevention. Sensitivity and specificity only depend on the risk limit of an algorithm after which, for example, it is decided to administer drugs.



## CONCLUSIONS

Our results reveal that the adapted REGICOR algorithm is the option applicable up to age 74 that gives the best balance in its capacity to classify risk of cardiovascular events in terms of sensitivity, specificity and positive predictive value of the risk algorithms available. Its application enables us to classify as high-risk, patients with a profile making them the best candidates for lipid-lowering drug treatment.

## REFERENCES

- Marrugat J, Elosúa R, Martí H. Epidemiología de la cardiopatía isquémica en España: estimación del número de casos y de las tendencias entre 1997 y 2005. *Rev Esp Cardiol*. 2002;55:337-46.
- Álvarez-León EE, Elosúa R, Zamora A, Aldasoro E, Galcerá J, Vanaclocha H, et al. Recursos hospitalarios y letalidad por infarto de miocardio. Estudio IBERICA. *Rev Esp Cardiol*. 2004;57:514-23.
- Gil M, Marrugat J, Sala J, Masiá R, Elosúa R, Albert X, et al, for the REGICOR Investigators. Relationship of Therapeutic Improvements and 28-Day Case Fatality in Patients Hospitalized With Acute Myocardial Infarction Between 1978 and 1993 in the REGICOR Study, Gerona, Spain. *Circulation*. 1999;99:1767-73.
- Sans S, Kesteloot H, Kromhout D. The burden of cardiovascular diseases mortality in Europe. Task force of the European Society of Cardiology on Cardiovascular Mortality and Morbidity Statistics in Europe. *Eur Heart J*. 1997;18:1231-48.
- Kannel WB, D'Agostino RB, Sullivan L, Wilson PW. Concept and usefulness of cardiovascular risk profiles. *Am Heart J*. 2004; 148:16-26.
- Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA*. 2004;291:2591-9.
- Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ*. 2003; 327: 1267-73.
- Empaña JP, Ducimetière P, Arveiler D, Ferrieres J, Evans A, Riudavets J, et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. *Eur Heart J*. 2003;24:1903-11.
- Hense HW, Schulte H, Lowel H, Assmann G, Keil U. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany—results from the MONICA Augsburg and the PROCAM cohorts. *Eur Heart J*. 2003;24:937-45.
- Marrugat J, D'Agostino R, Sullivan L, Elosúa R, Wilson P, Ordovas J, et al. An adaptation of the Framingham coronary heart disease risk function to European Mediterranean areas. *J Epidemiol Community Health*. 2003;57:634-8.
- de Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2003;24:1601-10.
- D'Agostino RB, Grundy S, Sullivan LM, Wilson P, for the CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180-7.
- Marrugat J, Solanas P, D'Agostino R, Sullivan L, Ordovas J, Cordon F, et al. Estimación del riesgo coronario en España mediante la ecuación de Framingham calibrada. *Rev Esp Cardiol*. 2003; 56:253-61.
- Ramos R, Solanas P, Cordón F, Rohlfis I, Elosúa R, Sala J, et al. Comparación de la función de Framingham original y la calibrada del REGICOR en la predicción del riesgo coronario poblacional. *Med Clin (Barc)*. 2003;121:521-6.
- Marrugat J, Subirana I, Comín E, Cabezas C, Vila J, Elosúa R, et al. For the VERIFICA (Validación de la Ecuación de Riesgo Individual de Framingham de Incidentes Coronarios Adaptada) Investigators. Validity of an adaptation of the Framingham cardiovascular risk function: the VERIFICA study. *J Epidemiol Comm Health*. 2007;61:40-7.
- Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837-47.
- Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, de Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987-1003.
- Masiá R, Pena A, Marrugat J, Sala J, Vila J, Pavesi M, et al, and the REGICOR investigators. High prevalence of cardiovascular risk factors in Gerona, Spain, a province with low myocardial infarction incidence. *J Epidemiol Comm Health*. 1998;52:707-15.
- Comité Español Interdisciplinario para la Prevención Cardiovascular. Guía Europea de Prevención Cardiovascular en la Práctica Clínica. Madrid: Ministerio de Sanidad y Consumo; 2004.
- Mostaza JM, Vicente I, Taboada M, Laguna F, Echániz A, Gracia Iglesias F, et al. La aplicación de las tablas del SCORE a varones de edad avanzada triplica el número de sujetos clasificados de alto riesgo en comparación con la función de Framingham. *Med Clin (Barc)*. 2005;124:487-90.
- Goldbourt U, Yaari S, Medalie JH. Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality. A 21-year follow-up of 8000 men. *Arterioscler Thromb Vasc Biol*. 1997;17: 107-13.
- Castelli WP, Doyle JT, Gordon T, Hames CG, Hjortland MC, Hulley SB, et al. HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study. *Circulation*. 1977;55:767-72.
- Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-34.
- Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ*. 2002;324:1-5.
- Lee CD, Folsom AR, Pankow JS, Brancati FL, for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. *Circulation*. 2004;109: 855-60.
- Jimeno J, Molist N, Franch J, Serrano V, Serrano L, Gracia R. Variabilidad en la estimación del riesgo coronario en la diabetes mellitus tipo 2. *Aten Primaria*. 2005;35:30-6.
- Katerndahl DA, Lawler WR. Variability in meta-analytic results concerning the value of cholesterol reduction in coronary heart disease: a meta-meta-analysis. *Am J Epidemiol*. 1999;149:429-41.
- Pignone M, Phillips C, Mulrow C. Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials. *BMJ*. 2000;321:1-5.
- Do statins have a role in primary prevention? Therapeutics letter (revista electrónica) 2003 April-May [accessed 12 Feb 2007]. Available from: <http://www.ti.ubc.ca/pages/letter48.htm>
- Miguel García F, García Ortiz A, Montero Alonso MJ. Prevención primaria con estatinas, consenso y tablas de riesgo. *Aten Primaria*. 2005;36:31-8.
- Jackson PR, Wallis EJ, Haq IU, Ramsay E. Statins for primary prevention: at what coronary risk is safety assured? *J Clin Pharmacol*. 2001;52:439-46.

Comín E et al. Algorithms of Cardiovascular Risk in Spain

32. Cucherat M, Lievre M, Gueyffier F. Clinical benefits of cholesterol lowering treatments. Meta-analysis of randomized therapeutic trials. *Presse Med.* 2000;29:965-76.
33. Vrečer M, Turk S, Drinovec J, Mrhar A. Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomised trials. *Int J Clin Pharmacol Ther.* 2003;41:567-77.