

## The ERICE-score: the new native cardiovascular score for the low-risk and aged mediterranean population of Spain

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### Abstract

#### *Introduction and objectives*

In Spain, data based on large population-based cohorts adequate to provide an accurate prediction of cardiovascular risk have been scarce. Thus, calibration of the EuroSCORE and Framingham scores has been proposed and done for our population. The aim was to develop a native risk prediction score to accurately estimate the individual cardiovascular risk in the Spanish population.

#### *Methods*

Seven Spanish population-based cohorts including middle-aged and elderly participants were assembled. There were 11 800 people (6387 women) representing 107 915 person-years of follow-up. A total of 1214 cardiovascular events were identified, of which 633 were fatal. Cox regression analyses were conducted to examine the contributions of the different variables to the 10-year total cardiovascular risk.

#### *Results*

Age was the strongest cardiovascular risk factor. High systolic blood pressure, diabetes mellitus and smoking were strong predictive factors. The contribution of serum total cholesterol was small. Antihypertensive treatment also had a significant impact on cardiovascular risk, greater in men than in women. The model showed a good discriminative power (C-statistic = 0.789 in men and C = 0.816 in women). Ten-year risk estimations are displayed graphically in risk charts separately for men and women.

#### *Conclusions*

The ERICE is a new native cardiovascular risk score for the Spanish population derived from the background and contemporaneous risk of several Spanish cohorts. The ERICE score offers the direct and reliable estimation of total cardiovascular risk, taking in consideration the effect of diabetes mellitus and cardiovascular risk factor management. The ERICE score is a practical and useful tool for clinicians to estimate the total individual cardiovascular risk in Spain.

### Resumen

#### *Introducción y objetivos*

En España no existen unas cohortes poblacionales suficientemente grandes para hacer predicciones precisas del riesgo cardiovascular. Las ecuaciones de Framingham y EuroSCORE calibradas son las más utilizadas en España. El objetivo es desarrollar la primera ecuación de predicción autóctona para estimar con precisión el riesgo cardiovascular individual en España.

#### *Métodos*

Análisis conjunto de siete cohortes españolas de población de mediana edad y anciana. La población del estudio — 11.800 personas (6.387 mujeres)— aportó un total de 107.915 personas-año de seguimiento y 1.214 eventos cardiovasculares (633 de ellos, mortales). Se efectuó un análisis de regresión de Cox para examinar la contribución de los diferentes factores al riesgo de cualquier evento cardiovascular (mortal y no mortal).

#### *Resultados*

La edad fue el principal factor de riesgo de eventos cardiovasculares. La presión arterial sistólica, la diabetes mellitus, el tabaquismo y el tratamiento antihipertensivo fueron factores predictivos fuertemente asociados con el riesgo cardiovascular. En cambio, la contribución del colesterol total sérico fue pequeña, especialmente en los mayores de 70 años. El modelo final de riesgo mostró un buen poder discriminatorio (estadístico C = 0,789 en varones y C = 0,816 en mujeres).

#### *Conclusiones*

ERICE es una nueva ecuación de riesgo cardiovascular genuinamente española obtenida a partir del riesgo concurrente individual de los participantes en varias cohortes. La ecuación ERICE ofrece una estimación directa y fiable del riesgo cardiovascular total teniendo en cuenta factores como la diabetes mellitus y el tratamiento farmacológico de los factores de riesgo cardiovascular, habitualmente no incluidos en otras ecuaciones.

**Keywords**

Risk score; Low-cardiovascular risk; Aging; Mediterranean; Diabetes mellitus; Spain

**Palabras clave**

Ecuación de riesgo; Bajo riesgo cardiovascular; Envejecimiento; Mediterráneo; Diabetes mellitus; España

**Abbreviations**

CHD, coronary heart disease; CVD, cardiovascular disease; ERICE, *Ecuación de Riesgo Cardiovascular Española*; ICD, International Classification of Diseases; SBP, systolic blood pressure; TC, total cholesterol

**Introduction**

Current recommendations on the prevention of cardiovascular disease (CVD) in clinical practice encourage health workers to assess the individual's total CVD risk rather than focus on a specific CVD outcome alone.<sup>1</sup>

Several risk calculators are available in Europe and the United States<sup>2, 3, 4 and 5</sup> but most of them have been only validated in middle-aged populations or in areas with a relatively high coronary heart disease (CHD) risk and they do not account for the effect of medications used for risk factor management.<sup>6, 7 and 8</sup> Although calibration of these foreign scores have been done in countries with lower CHD rates such as China and Spain and validated in the VERIFICA Study<sup>8</sup>. However, until now we did not have a native scale of cardiovascular risk based on the follow-up of large cohorts and derived from the same population where it will be later administered. In most of the Southern European countries, however, no sufficiently large population-based cohorts existed thus far to provide accurate and reliable estimates of the CVD risk by age and sex<sup>9</sup>. Furthermore, the impact of diabetes mellitus (DM) that is an important aspect to be considered in the CVD risk assessments has not been included in the available European risk scores leaving out the potential impact of DM when assessing CVD risk in clinical practice.<sup>2</sup>

The existing risk scores vary widely in terms of the background risk in study populations, predictors and outcomes considered (the Framingham score focuses on the CHD incidence and the SCORE (Systematic COronary Risk Evaluation) function on CVD mortality rather than the total CVD risk). Most can be used up to the age of 75 years. The scores do not take into account the possible effects of pharmacological risk factor management in the study population and will therefore underestimate the actual cardiovascular risk. The SCORE function does not include DM as a risk factor, and the Framingham algorithm underestimates its impact.

In addition, most of the existing scores were derived from cohorts of primarily middle-aged people at baseline, leaving older persons underrepresented. For example, the SCORE function concentrates on middle-aged people and is only recommended for use in the age range of 40 to 65 years.<sup>4</sup> The estimation of cardiovascular risk in people > 70 years is problematic because the predictive power of classical CVD risk factors decreases with age. For instance, the Framingham score seems to be of limited utility for elderly people, according to the Leiden 85-plus study, which showed a very poor discrimination, with the area under the curve in the receiver operating characteristics calculation only 0.53 (95% confidence interval [95%CI], 0.43-0.64)<sup>7</sup>

According to the guidelines of the Fourth Joint Task Force,<sup>2</sup> it is important to develop a European CVD risk score adapted to specific geographical areas and to include individuals at older ages that will allow a more precise identification of asymptomatic individuals at high risk of CVD and a more effective implementation of the preventive interventions targeted to lower the total CVD risk. Hence, there is a place for a new CVD score that overcomes some of the limitations of previous tools.

The aim of this study is to develop a new CVD risk assessment tool that will accurately predict the individual risk of total CVD in the population of Spain.

## Methods

### Data Sources

The ERICE (*Ecuación de Riesgo Cardiovascular Española*) project comprised seven population-based cohort studies in different geographical areas of Spain. The designs of the original studies have been detailed elsewhere.<sup>10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20</sup> A collaborative database was created with the individual data from all participants in these 7 cohorts (Table 1).

**Table 1.** Characteristics of the Cohorts Included in the ERICE Project

Study	Location	Study population, no.			Age, mean (SD) [age range at baseline, y]	Year of recruitment, follow-up, mean (SD), y	Follow up, person-years	Number of cases lost to follow-up
		Men	Women	Total				
EPICARDIAN <sup>11 and 12</sup>	Madrid, Lugo, Avila (center, northwest)	1463	2015	3478	74 (6.8) [> 65]	1994 (8.0 [3.0])	27 789	2 (0.1)
VIVA <sup>13 and 14</sup>	Lugo, Barcelona (northwest, northeast)	365	374	739	48.9 (9.1) [35-64]	1996 (9.4 [1.2])	6963	33 (4.5)
REGICOR <sup>17</sup>	Girona (northeast)	765	846	1611	52.4 (12.7) [30-74]	1994/1996 (6.7 [1.2])	10 756	83 (5.2)
CORSAIB <sup>15</sup>	Mallorca (east)	736	833	1569	53.3 (11.3) [35-74]	1999 (7.4 [1.2])	11 549	0 (0.0)
Talavera <sup>19</sup>	Toledo (centre)	561	627	1188	54.8 (13.3) [30-74]	1994 (9.5 [2.0])	11 283	21 (1.8)
Albacete <sup>18</sup>	Albacete (southeast)	450	534	984	53.1 (14.6) [> 30]	1992 (11 [2.2])	10 834	0 (0.0)
Murcia <sup>20</sup>	Murcia (southeast)	1073	1158	2231	44.8 (10.2) [30-65]	1991 (12.9 [2])	28 741	245 (11.0)
Total		5413	6387	11 800	57.6 (15.4) [> 30]	(9.1 [3.1])	107 915	384 (3.3)

Vital status was ascertained for 100% of participants.

Lost to follow-up was considered when there was no information about the vital status when the cohort was closed.

Unless otherwise indicated, data are expressed as No. (%) or mean (standard deviation).

The studies had to meet the following criteria: single or multicenter surveys of general adult population of both sexes aged  $\geq 20$  years; a clear description of the target population and the sampling methods, a random selection of participants, an adequate participation in the baseline survey ( $> 60\%$ ), a sufficiently long follow-up, a small number of participants lost to follow-up, a description of standardized measurement of clinical variables (blood pressure, blood lipids, smoking, and fasting plasma glucose) and a reliable method of assessing CVD events during the follow-up. In this analysis, only individuals aged  $\geq 30$  years and free of clinical CVD at baseline were included.

### Measurement and Definition of Cardiovascular Risk Factors

The CVD risk factors were assessed at baseline examination. The final common database included the following study variables: age, sex, place of residence, body mass index, systolic blood pressure (SBP), diastolic blood pressure, cigarette consumption, total serum total cholesterol (TC), fasting or random glucose, and personal history of hypertension, hypercholesterolemia, DM, and drug treatment for hypertension, hypercholesterolemia, and DM. Whole blood and capillary glucose values were converted to plasma values using the formula proposed by Carstensen et al.<sup>21</sup> For the development of Cox models, the independent variables were categorized as follows: age was grouped in 10-year categories except for women  $< 50$  years, because there were few cardiovascular events in this age- group. Systolic blood pressure was categorized:  $< 140$  mmHg; 140-159 mmHg; 160-179 mmHg;  $\geq 180$  mmHg. Categories for TC were:  $< 5.2$  mmol/L, 5.2-6.4 mmol/L, 6.5-7.7 mmol/L and  $\geq 7.8$  mmol/L. The smoking status was categorized as nonsmokers and smokers (including exsmokers who had stopped smoking  $< 6$  months earlier and those who smoked at baseline).

Hypertension was considered when SBP  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg or treatment with antihypertensive drugs.<sup>22</sup> Hypercholesterolemia was considered when TC  $\geq 5.1$  mmol/L or treatment with lipid-lowering drugs.<sup>23</sup> Diabetes mellitus was defined as fasting venous plasma glucose  $\geq 7.0$  mmol/L, random capillary glucose  $\geq 11.1$  mmol/L or treatment with oral antidiabetic drugs or

insulin at baseline. Body mass index was calculated for each individual using the formula of weight in kilograms divided by the square of height in meters, and obesity was defined as body mass index  $\geq 30$ .

#### *Follow-up and Cardiovascular Events*

Information on CVD events was collected by searching all potential sources (primary care and hospital records, interviews with general practitioners, National Institute of Statistics, mailings, and phone calls to the participants or their relatives). The date and cause of death of each deceased individual in the cohort was also confirmed through the Spanish National Death Index and the mortality registries of each autonomic community.

#### *Cardiovascular Disease Event Registration*

Using the International Classification of Diseases (ICD-9 and ICD-10), causes of death were defined as CHD (ICD-9: 410-414, ICD-10: I20-I25), cerebrovascular disease (ICD-9: 430-434, 436-438; ICD-10: I58-I61), and other potential cardiovascular conditions (ICD-9: 797-799; ICD-10: I46, R96, R98, I50).

#### *Cardiovascular Disease Event Classification*

Coronary events were classified following the World Health Organization MONICA Project<sup>24</sup> algorithm adapted by the REGICOR.<sup>25</sup> Cerebrovascular cases were classified following the MONICA stroke study algorithm.<sup>26</sup>

Cardiovascular disease is a composite of first “hard” coronary event (definite fatal and nonfatal myocardial infarction and possible fatal myocardial infarction) or cerebrovascular event (including acute ischemic stroke and other nondetermined stroke events).

#### *Statistical Methods*

For the description of the selected data, arithmetic mean (standard deviation) was used when the variables were continuous and relative frequency distribution when categorical. For comparison of proportions, the Pearson chi-square test and the Sommer D were used in the case of ordinal variables. For group comparison, the Student-Fisher *t* test was used in the case of independent binary measures and analysis of variance for variables of more than 2 categories.

#### *Multivariate Models and Estimation of General Cardiovascular Disease Risk Functions*

To analyze the association between each independent variable collected (age, sex, SBP, diastolic blood pressure, smoking, DM, TC, serum high-density lipoprotein cholesterol, and triglycerides) and the outcome variables, both bivariate and multivariate analyses were performed. Due to the precise data available about risk factor treatments, modeling the impact of a participant's SBP or TC levels with or without pharmacological treatment for these two risk factors was possible.

Cox regression analyses were conducted to identify and examine the contributions of the different variables for CVD as the potential basis for the ERICE-score. Coefficients independently associated with each potential risk factor for the first recorded CVD event were estimated separately for men and women. A Kaplan-Meier extrapolation of the first fatal or nonfatal CVD event during the 10-year period was performed to calculate the overall mean ERICE cumulative incidence of the CVD event. To estimate the survival function, analysis was performed using Kaplan-Meier method stratified by sex and age ( $\leq 70$  years or  $> 70$  years). Cox models were also adjusted by the study cohort. Omnibus test was used to validate the model ( $P < .05$ ). Sex-specific risk score sheets for CVD event prediction using categorical variables were developed from the  $\beta$ -coefficients of Cox proportional hazards models.

A graphical inspection of the proportionality of the hazard assumption was carried out. Possible violations of the proportional hazards assumption in Cox regression were assessed using graphical methods. In addition, the model assumptions were tested for compliance.

We split the ERICE score into 6 categories of total 10-year CVD risk: low risk:  $< 5\%$ ; mild risk:  $5\%$  to  $9\%$ ; moderate risk:  $10\%$  to  $14\%$ ; moderate-high risk:  $15\%$  to  $19\%$ ; high risk:  $20\%$  to  $29\%$ , and very high risk:  $\geq 30\%$ .

## *Ethics*

Our research is in compliance with the Helsinki Declaration. All individual studies obtained informed consent of the participants at baseline examination, and all studies were approved by the local ethics committees.

## **Results**

### *Characteristics of the Study Population*

There were 11 800 participants (5413 men and 6387 women) representing 107 915 person-years of follow-up. The median follow-up for the entire study was 9.1 years. A complete follow-up was reported in 11 416 people (96.7% of the total population; 5235 men and 6181 women). We were able to assess the vital status of 100% of cohort participants (Table 1).

Table 2 shows the cardiovascular risk factors and events distribution by sex and study cohort. In total, 1214 CVD events occurred in the entire cohort during the 10-year follow-up period (638 in men and 576 in women), of which 633 were CVD deaths (325 in men and 308 in women). The distribution by sex of the CVD risk factor categories in the ERICE study is detailed in Table 1 of supplementary material. Variables such as diastolic blood pressure, body mass index, and lipid-lowering medication were not statistically associated with CVD (Table 2 of supplementary material), and there were only some participants with data available for triglycerides and high-density lipoprotein cholesterol (only one third of the participants).

**Table 2.** Risk Factor Information and Events by Sex and Study Cohort

Study	No.	Age at baseline, mean (SD), y	Smokers, %	BMI, mean (SD)	Obesity, %	HDL-C, mean (SD), mmol/L	TC, mean (SD), mmol/L	Hypercholesterolemia, %	FPG, mean (SD), mmol/L	DM, %	(SD), mmHg	HT, %	Total No. of deaths (all causes)	First CV events (fatal events), No.	Cumulative incidence, % (follow-up, mean [SD]), y
<i>Total men</i>	5413	56.9 (15.2)	61.9	27.1 (3.8)	20.8	1.3 (0.4)	5.5 (1.1)	18.1	5.7 (1.6)	8.8	136.2 (19.5)	48.7	1107	638 (325)	11.79 (8.9 [3.2])
EPICARDIAN <sup>11 and 12</sup>	1463	73.7 (6.6)	74.2	26.9 (3.9)	19.1	1.2 (0.3)	5.4 (1.2)	18.2	5.9 (1.7)	10.7	143.0 (19.6)	64.1	703	356 (222)	24.33 (7.5 [3.2])
VIVA <sup>13 and 14</sup>	365	48.6 (9.1)	72.9	27.1 (3.6)	20.3	1.2 (0.3)	5.7 (1.0)	20.5	5.6 (1.1)	5.5	124.2 (18.4)	26.3	17	15 (5)	4.11 (9.3 [1.4])
REGICOR <sup>17</sup>	765	52.7 (12.8)	65.3	26.7 (3.7)	18.4	1.2 (0.4)	5.8 (1.1)	25.8	5.9 (1.5)	10.3	134.0 (19.5)	41.6	52	33 (9)	4.31 (6.5 [1.3])
CORSAIB <sup>15</sup>	736	53.3 (11.5)	36.5	27.5 (4.0)	23.6	1.2 (0.3)	5.6 (1.1)	20.5	5.9 (1.8)	14.9	136.1 (18.8)	50.8	74	57 (20)	7.74 (7.2 [1.5])
Talavera <sup>19</sup>	561	55.3 (13.3)	36.9	27.3 (3.8)	22.3	1.2 (0.3)	5.5 (1.0)	15.5	5.2 (1.7)	7.1	137.9 (19.4)	47.4	92	66 (33)	11.76 (9.2 [2.3])
Albacete <sup>18</sup>	450	52.1 (14.5)	67.1	27.5 (4.0)	23.6	—	5.4 (1.0)	13.6	5.7 (1.6)	8.4	133.9 (19.3)	47.1	67	38 (13)	8.44 (10.8 [2.4])
Murcia <sup>20</sup>	1073	45.0 (10.5)	67.5	27.2 (3.6)	21.0	1.5 (0.4)	5.3 (1.1)	13.3	—	3.4*	132.5 (17.2)	40.1	102	73 (23)	6.80 (12.7 [2.3])
<i>Total women</i>	6387	58.1 (15.5)	15.2	27.8 (5.1)	29.6	1.5 (0.4)	5.6 (1.1)	20.9	5.6 (1.7)	8.4	136.0 (22.5)	50.8	875	576 (308)	9.02 (9.4 [2.9])
EPICARDIAN <sup>11 and 12</sup>	2015	74.3 (6.9)	8.0	27.7 (5.0)	29.4	1.3 (0.3)	5.9 (1.2)	29.9	5.9 (1.9)	12.1	146.9 (20.6)	74.3	638	412 (235)	20.45 (8.4 [2.8])
VIVA <sup>13 and 14</sup>	374	49.3 (9.1)	16.1	27.1 (4.7)	25.4	1.5 (0.3)	5.7 (1.0)	20.3	5.2 (1.2)	3.5	124.4 (19.9)	27.8	6	8 (0)	2.14 (9.5 [1.0])
REGICOR <sup>17</sup>	846	52.2 (12.6)	18.7	26.6 (4.5)	19.9	1.5 (0.4)	5.8 (1.1)	25.1	5.6 (1.5)	7.2	129.7 (20.9)	38.4	31	16 (9)	1.89 (6.9 [1.0])
CORSAIB <sup>15</sup>	833	53.3 (11.1)	19.2	27.6 (5.3)	29.1	1.5 (0.3)	5.6 (1.0)	19.4	5.5 (1.5)	8.4	131.3 (22.2)	43.3	29	30 (5)	3.60 (7.5 [1.0])
Talavera <sup>19</sup>	627	54.3 (13.3)	12.8	29.4 (5.3)	40.2	1.3 (0.3)	5.6 (1.0)	17.9	5.1 (1.7)	7.3	135.7 (21.9)	45.8	61	42 (22)	6.70 (9.8 [1.7])
Albacete <sup>18</sup>	534	53.9 (14.6)	16.3	28.6 (5.3)	35.8	—	5.3 (0.9)	10.5	5.7 (1.9)	10.9	137.7 (23.4)	51.7	47	31 (17)	5.81 (11.2 [2.0])
Murcia <sup>20</sup>	1158	44.7 (10.0)	22.6	28.1 (4.9)	30.1	1.7 (0.5)	5.0 (1.1)	9.7	—	4.1*	128.3 (19.9)	33.9	63	37 (20)	3.20 (13.1 [1.5])
<i>Total ERICE</i>	11800	57.5 (15.4)	36.6	27.5 (4.6)	25.5	1.4 (0.4)	5.5 (1.1)	19.6	5.6 (1.7)	8.6	136.1 (21.2)	49.8	1982	1214 (633)	10.3 (9.1 [3.1])

BMI, body mass index; CV, cardiovascular; DM, diabetes mellitus; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; HT, hypertension; TC, total cholesterol.

Hypertension: systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or antihypertensive treatment.

Diabetes mellitus: fasting plasma glucose > 7 mmol/L, random capillary glycaemia > 11 mmol/L or antidiabetic treatment.

Hypercholesterolemia: total cholesterol > 6.5 mmol/L or lipid-lowering treatment.

Obesity: body mass index > 30 kg/m<sup>2</sup>.

Unless otherwise indicated, data are expressed as mean (standard deviation).

\*Self-reported.

The multivariate adjusted hazard ratios (HR) of CVD for the different cardiovascular risk factors included in the final Cox model in men and women are shown in Table 3 and Table 4. Antihypertensive drug treatment had a significant impact, greater in men than in women. Elevated serum cholesterol increased the risk of acute coronary event in men (HR = 1.50; 95%CI, 1.02-2.19) and women (HR = 3.64; 95%CI, 1.64-8.11) aged < 70 years, but at older ages the risk did not increase. Elevated serum cholesterol did not significantly increase the risk of cerebrovascular disease.

**Table 3.** Multivariate Cox Model for a First Fatal or Nonfatal Average 10-year Cardiovascular Event. Men

	No. (total events, no.)	$\beta$	SE	HR	95%CI	P
<b>Age at baseline (age groups)</b>						
40-49	964 (25)	0.638	0.343	1.89	0.97-3.71	.063
50-59	788 (59)	1.681	0.310	5.37	2.93-9.90	<.001
60-69	1323 (208)	2.402	0.299	11.04	6.15-19.83	<.001
70-79	963 (223)	2.862	0.310	17.50	9.54-32.12	<.001
$\geq 80$	309 (110)	3.519	0.323	33.75	17.91-63.58	<.001
<b>Smoker<sup>a</sup></b>						
Yes	3209 (428)	0.282	0.092	1.33	1.11-1.59	.002
<b>SBP (mmHg)</b>						
<i>No treated</i>						
140-159	1141 (181)	0.407	0.107	1.50	1.22-1.85	<.001
160-179	342 (61)	0.490	0.150	1.63	1.22-2.19	.001
$\geq 180$	75 (15)	0.552	0.270	1.74	1.02-2.95	.041
<i>Treated</i>						
< 140	225 (54)	0.753	0.158	2.12	1.56-2.90	<.001
140-159	295 (67)	0.585	0.146	1.80	1.35-2.39	<.001
160-179	187 (53)	0.850	0.160	2.34	1.71-3.20	<.001
$\geq 180$	69 (22)	0.925	0.230	2.52	1.61-3.96	<.001
<b>Total cholesterol (mmol/L)</b>						
5.2-6.4	2243 (275)	0.018	0.089	1.02	0.86-1.21	.835
6.5-7.7	764 (101)	0.068	0.119	1.07	0.85-1.35	.570
$\geq 7.8$	131 (14)	-0.041	0.276	0.96	0.56-1.65	.881

95%CI, 95% confidence interval; HR, hazard ratio; SBP: systolic blood pressure; SE, standard error.

Category of reference: young (men 30-39 years old; women 30-49 years old), nonsmoker, nondiabetics, nontreated with antihypertensive drugs, systolic blood pressure < 140 mmHg, total cholesterol < 5.2 mmol/L.

Model was adjusted by the cohort effect.

Harrel C-statistic = 0.792.

a Smoker: current smoker and exsmoker ( $\leq 6$  months).

b Diabetic: fasting plasma glucose > 7 mmol/L or treatment with insulin or oral antidiabetic drugs at baseline.

**Table 4.** Multivariate Cox Model for a First Fatal or Nonfatal Average 10-year Cardiovascular Event. Women

	No. (total events, no.)	$\beta$	SE	HR	95%CI	<i>P</i>
<b>Age at baseline (age groups)</b>						
50-59	908 (38)	2119	0.330	8.32	4.36-15.89	<.001
60-69	1494 (132)	2739	0.318	15.47	8.30-28.84	<.001
70-79	1245 (227)	3471	0.329	32.18	16.87-61.38	<.001
$\geq 80$	472 (166)	4368	0.339	78.86	40.58-153.22	<.001
<b>Smoker<sup>a</sup></b>						
Yes	910 (46)	0.407	0.159	1.50	1.10-2.05	.011
<b>Diabetic</b>						
Yes	530 (98)	0.446	0.113	1.56	1.25-1.95	<.001
<b>SBP (mmHg)</b>						
<i>No treated</i>						
140-159	1106 (147)	0.065	0.124	1.07	0.84-1.36	.603
160-179	321 (32)	-0.121	0.197	0.89	0.60-1.30	.540
$\geq 180$	79 (19)	0.449	0.248	1.57	0.96-2.55	.070
<i>Treated</i>						
< 140	384 (55)	0.272	0.160	1.31	0.96-1.79	.089
140-159	605 (93)	0.193	0.136	1.21	0.93-1.58	.157
160-179	392 (68)	0.178	0.151	1.19	0.89-1.61	.241
$\geq 180$	159 (34)	0.355	0.195	1.43	0.97-2.09	.068
<b>Total cholesterol (mmol/L)</b>						
5.2-6.4	2628 (254)	0.014	0.100	1.01	0.83-1.23	.892
6.5-7.7	1058 (131)	-0.024	0.118	0.98	0.77-1.23	.840
$\geq 7.8$	188 (20)	-0.227	0.244	0.80	0.49-1.28	.352

95%CI, 95% confidence interval; HR, hazard ratio; SBP: systolic blood pressure; SE, standard error.

Category of reference: young (men 30-39 years old; women 30-49 years old), nonsmoker, nondiabetics, nontreated with antihypertensive drugs systolic blood pressure < 140 mmHg, total cholesterol < 5.2 mmol/L.

Model was adjusted by the cohort effect.

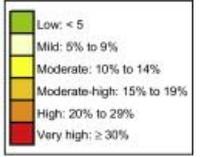
Harrel C-statistic = 0.819.

a Smoker: current smoker and exsmoker ( $\leq 6$  months).

b Diabetic: fasting plasma glucose > 7 mmol/L or treatment with insulin or oral antidiabetic drugs at baseline.

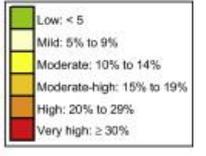
The entire model showed a good discriminative power (C-statistic = 0.789 in men and C = 0.816 in women). Score sheets were developed to predict CVD events in men and women from the  $\beta$ -coefficients of Cox proportional hazard models. Figure 1, Figure 2, Figure 3 and Figure 4 show the 10-year risk of a fatal and nonfatal CVD event in men and women with and without antihypertensive treatment.

		Men without antihypertensive treatment								Men without antihypertensive treatment								
		Diabetics				Non diabetics				Diabetics				Non diabetics				
		Non smokers				Smokers				Non smokers				Smokers				
		< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	
≥ 80	SBP	≥ 180	56	57	58	55	66	67	69	65	48	47	48	45	56	57	58	55
		160-180	54	54	56	52	64	65	67	63	44	45	46	43	54	54	56	52
		140-160	51	51	53	49	61	62	64	60	41	42	44	40	51	51	53	49
		< 140	38	38	40	36	47	47	49	45	30	30	32	30	38	38	40	36
70-79	SBP	≥ 180	35	35	37	34	43	44	45	42	27	28	29	27	35	35	37	34
		160-180	33	33	35	32	41	42	43	40	26	26	28	25	33	33	35	32
		140-160	31	31	33	30	39	39	41	37	24	25	26	23	31	31	33	30
		< 140	22	22	23	21	28	28	29	27	17	17	18	16	22	22	23	21
60-69	SBP	≥ 180	24	24	25	23	30	30	32	32	18	19	19	18	24	24	25	23
		160-180	22	23	24	22	28	29	30	30	17	18	18	17	22	23	24	22
		140-160	21	21	22	20	27	27	28	26	16	16	17	15	21	21	22	20
		< 140	14	15	15	15	19	19	19	18	11	11	12	11	14	15	15	15
50-59	SBP	≥ 180	12	12	13	12	16	16	17	15	9	10	10	10	12	12	13	12
		160-180	12	12	12	11	15	15	16	16	9	9	9	9	12	12	12	11
		140-160	11	11	11	10	14	14	14	13	8	8	8	8	11	11	11	10
		< 140	7	7	8	7	9	10	10	9	6	6	6	5	7	7	8	7
40-49	SBP	≥ 180	5	5	5	5	6	6	6	6	3	3	4	3	4	5	5	5
		160-180	4	4	5	5	6	6	6	5	3	3	3	3	4	4	5	5
		140-160	4	4	4	4	5	5	5	5	3	3	3	3	4	4	4	4
		< 140	3	3	3	3	3	4	4	3	2	2	2	2	3	3	3	3
30-39	SBP	≥ 180	2	2	3	2	3	3	3	3	2	2	2	2	2	2	3	2
		160-180	2	2	2	2	3	3	3	3	2	2	2	2	2	2	2	2
		140-160	2	2	2	2	3	3	3	3	2	2	2	2	2	2	2	2
		< 140	1	1	1	1	2	2	2	2	1	1	1	1	1	1	1	1
Cholesterol		< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	



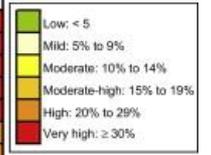
**Figure 1.** Ten-year absolute risk of a first fatal or nonfatal cardiovascular event. Men without antihypertensive treatment. DBP, diastolic blood pressure; SBP, systolic blood pressure.

		Men with antihypertensive treatment								Men with antihypertensive treatment								
		Diabetics				Non diabetics				Diabetics				Non diabetics				
		Non smokers				Smokers				Non smokers				Smokers				
		< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	
≥ 80	SBP	≥ 180	70	70	72	68	79	80	82	78	59	60	62	58	70	70	72	68
		160-180	67	68	69	65	77	78	79	76	57	57	59	55	67	68	69	65
		140-160	57	58	60	56	68	68	70	66	47	48	50	46	57	58	60	56
		< 140	63	64	66	62	74	74	76	72	53	54	56	52	63	64	66	62
70-79	SBP	≥ 180	46	47	48	45	56	57	58	54	37	38	39	36	46	47	48	45
		160-180	44	44	46	42	53	54	56	52	35	36	37	34	44	44	46	42
		140-160	36	36	38	34	44	45	46	43	30	30	30	30	36	36	38	34
		< 140	41	41	43	39	50	50	52	48	32	33	34	31	41	41	43	39
60-69	SBP	≥ 180	32	33	34	31	40	41	43	39	25	26	27	25	32	33	34	31
		160-180	30	31	32	30	38	39	40	37	24	24	25	23	30	31	32	30
		140-160	24	25	26	23	31	31	33	30	20	20	20	20	24	25	26	23
		< 140	28	28	29	27	35	36	37	34	22	22	23	21	28	28	29	27
50-59	SBP	≥ 180	17	18	18	17	22	23	24	21	13	14	14	13	17	18	18	17
		160-180	16	16	17	16	21	21	22	20	12	13	13	12	16	16	17	16
		140-160	15	15	16	16	16	17	17	16	10	10	10	10	13	13	13	12
		< 140	15	15	16	16	19	19	19	18	11	12	12	11	14	14	14	14
40-49	SBP	≥ 180	6	7	7	6	8	9	9	8	5	5	5	5	6	7	7	6
		160-180	6	6	6	6	8	8	8	8	5	5	5	5	6	6	6	6
		140-160	5	5	5	5	6	6	7	6	4	4	4	4	5	5	5	5
		< 140	5	6	6	5	7	7	8	7	4	4	4	4	5	6	6	5
30-39	SBP	≥ 180	3	4	4	3	5	5	5	5	3	3	3	3	4	4	4	3
		160-180	3	3	3	3	4	4	5	5	2	2	2	2	3	3	3	3
		140-160	2	3	3	2	3	3	4	3	2	2	2	2	2	3	3	3
		< 140	3	3	3	3	4	4	4	4	2	2	2	2	3	3	3	2
Cholesterol		< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	



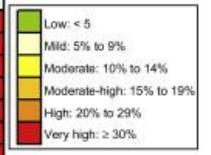
**Figure 2.** Ten-year absolute risk of a first fatal or nonfatal cardiovascular event. Men with antihypertensive treatment. DBP, diastolic blood pressure; SBP, systolic blood pressure.

		Women without antihypertensive treatment								Women without antihypertensive treatment								
		Diabetics				Non diabetics				Diabetics				Non diabetics				
		Non smokers				Smokers				Non smokers				Smokers				
Cholesterol		< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	
≥ 80	SBP	≥ 180	70	71	69	62	84	64	63	77	54	55	53	46	69	69	66	61
		160-180	50	50	49	42	64	65	64	56	36	36	35	30	48	49	48	41
		140-160	56	57	55	48	71	72	70	63	41	42	40	34	55	55	54	47
		< 140	54	54	53	46	69	69	66	60	39	40	38	33	53	53	52	45
70-79	SBP	≥ 180	39	39	38	33	53	53	52	46	27	28	27	22	38	38	37	32
		160-180	24	25	24	20	34	35	34	30	16	17	16	15	24	24	23	20
		140-160	29	29	28	24	40	40	39	33	19	19	19	16	28	28	27	23
		< 140	27	27	27	22	38	38	37	32	18	19	18	15	26	27	26	22
60-69	SBP	≥ 180	21	21	21	20	29	29	29	25	14	14	14	11	20	21	20	20
		160-180	13	13	12	10	18	19	18	15	8	8	8	7	12	12	12	10
		140-160	14	14	14	12	19	19	19	18	9	9	9	8	14	14	14	12
		< 140	14	14	14	11	19	19	19	17	9	9	9	7	14	14	13	11
50-59	SBP	≥ 180	12	12	12	10	18	18	17	15	8	8	8	6	12	12	11	10
		160-180	7	7	7	6	10	10	10	5	5	5	5	7	7	7	5	
		140-160	8	8	8	7	12	12	12	10	5	6	5	5	8	8	8	6
		< 140	8	8	8	6	12	12	11	10	5	5	5	5	8	8	7	6
30-49	SBP	≥ 180	2	2	1	1	2	2	2	2	1	1	1	1	1	1	1	1
		160-180	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
		140-160	1	1	1	1	2	2	2	1	1	1	1	1	1	1	1	1
		< 140	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Cholesterol		< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	



**Figure 3.** Ten-year absolute risk of a first fatal or nonfatal cardiovascular event. Women without antihypertensive treatment. DBP, diastolic blood pressure; SBP, systolic blood pressure.

		Women with antihypertensive treatment								Women with antihypertensive treatment								
		Diabetics				Non diabetics				Diabetics				Non diabetics				
		Non smokers				Smokers				Non smokers				Smokers				
Cholesterol		< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	
≥ 80	SBP	≥ 180	67	67	66	59	81	81	80	73	51	51	50	43	65	66	65	57
		160-180	60	61	60	52	75	76	74	67	45	45	44	38	59	59	58	51
		140-160	61	61	60	53	76	76	75	68	45	46	44	38	60	60	59	51
		< 140	64	64	63	56	78	79	78	70	48	48	47	41	62	63	62	54
70-79	SBP	≥ 180	36	37	36	30	49	50	48	42	25	25	25	21	35	36	35	30
		160-180	31	32	31	30	43	44	43	36	21	22	21	20	30	31	30	30
		140-160	32	32	31	30	44	44	43	37	22	22	21	20	31	31	30	30
		< 140	34	34	33	30	46	47	46	39	23	24	23	20	33	33	32	30
60-69	SBP	≥ 180	19	19	19	16	28	28	27	23	13	13	13	10	19	19	18	15
		160-180	17	17	16	15	24	24	23	20	11	11	11	10	16	16	16	15
		140-160	17	17	16	15	24	25	24	20	11	11	11	10	16	16	16	15
		< 140	18	18	18	15	26	26	25	21	12	12	12	10	17	18	17	15
50-59	SBP	≥ 180	11	11	11	10	16	16	16	15	7	7	7	6	11	11	10	10
		160-180	9	9	9	7	14	14	13	11	6	6	6	5	9	9	9	7
		140-160	9	9	9	8	14	14	14	11	6	6	6	5	9	9	9	7
		< 140	9	9	9	8	14	14	14	12	7	7	6	5	9	9	9	8
30-49	SBP	≥ 180	1	1	1	1	2	2	2	2	1	1	1	1	1	1	1	1
		160-180	1	1	1	1	2	2	2	1	1	1	1	1	1	1	1	1
		140-160	1	1	1	1	2	2	2	1	1	1	1	1	1	1	1	1
		< 140	1	1	1	1	2	2	2	2	1	1	1	1	1	1	1	1
Cholesterol		< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	< 5.2	5.2-6.4	6.5-7.7	≥ 7.8	



**Figure 4.** Ten-year absolute risk of a first fatal or nonfatal cardiovascular event. Women with antihypertensive treatment. DBP, diastolic blood pressure; SBP, systolic blood pressure.

## Discussion

The ERICE-score is unique in being based on a large cohort of 11 800 Spanish adults, covering a wide age range with uniform and harmonized baseline data. In contrast to previous scores such as the Framingham and EuroSCORE that were based on populations recruited before the 1990s, our estimates are based on more recent cohorts and offer different charts for individuals treated with antihypertensive drugs or not. The CVD incidence rates of this study stress the need of improving primary prevention measures, as more than half of the first CVD events resulted in death; the high case-fatality of coronary and stroke events is known also from previous studies.

### *Components of the Risk Score*

Age is the strongest predictor of CVD risk in both men and women. Despite the influence of age, favorable levels of all modifiable CVD risk factors assure a minimal CVD risk in a Mediterranean population aged < 70 years.<sup>9</sup>

Our results show that a completely different pattern is observed between the two sexes with regard to modifiable cardiovascular risk factors. In men, high SBP is the strongest predictive CVD risk factor, followed by DM and smoking with similar impacts. In women, DM plays a crucial role, followed by smoking and very high SBP (>180 mmHg). Antihypertensive drug treatment has a greater impact in men than in women. Contribution of high TC levels to the cardiovascular risk was small both in men and women. These results are in keeping with previous findings regarding the CVD risk in the Spanish population.<sup>27</sup> Also, we confirm that it is important to derive the CVD prediction model in the same population where the risk score will be later administered.<sup>28</sup>

### *Comparison With Previous Risk Estimates*

To date, the CVD prediction charts used to predict a CVD event in Spain have relied on risk estimates based on American (REGICOR)<sup>5, 29 and 30</sup> or European (SCORE)<sup>7 and 31</sup> populations, and the scores adapted for Spain have had important limitations as they came from small population samples, most of them based on occupational cohorts and geographically limited to the north east area of Spain.<sup>32, 33 and 34</sup> Another important limitation of previous estimates is that they are limited to CHD risk or CVD deaths. By calculating total CVD risk, we provide a better estimate of overall individual risk in a European region with low rates of CHD, such as Spain.

Moreover, previous estimates do not include DM at all or, as the Framingham algorithm, are based on a small number of DM people (4%, since diabetes at the time of the Framingham study's baseline data collection was not as common as more recently) and used its own definition of DM. ERICE-charts, following the recommendations of the Joint Task Force of the European Societies,<sup>1</sup> include a representative number of people with DM and give separate risk charts for this risk factor.

Finally, the ERICE-charts uniquely include cells for individuals aged 70 years to 79 years and  $\geq 80$  years, since the cohort included a large proportion of people > 75 years and accounted for the use of risk-factor-modifying drugs, which allows the resolution of a major gap in previous risk assessment tools.<sup>6</sup> Nevertheless, estimating the 10-year mortality risk in people aged  $\geq 80$  years of limited use. In Europe, especially in the south, life expectancy is increasing markedly. Therefore, it is necessary to start to pay more attention to CVD risk in the very elderly. It has been shown that people aged  $\geq 80$  years will benefit from preventive interventions, such as antihypertensive drug treatment if hypertensive.<sup>35</sup> Further analysis to explore 5-year risk estimation will be done in the near future, based on the elderly people included in this project. Other investigators also have started to develop risk scores in elderly cohorts.<sup>7</sup>

### *Limitations and Strengths*

The ERICE charts only consider the major CVD risk factors but, in practice, other factors (family history, high-density lipoprotein cholesterol, fibrinogen, physical exercise, waist circumference, etc.) can also modulate the CVD risk. People lost to follow-up were younger, and there were more smokers among female participants. No other significant differences in the distribution of risk factors were observed and thus the selection bias is minimal. High-density lipoprotein cholesterol measurement methods are different from one center to another, and this could have influenced the involvement of this factor in risk estimations. The Murcia cohort did not have data on blood glucose levels but information about drug treatment for DM was recorded. The predictive value of classical risk factors, such as hypercholesterolemia and systolic HT, weakens with age<sup>36 and 37</sup>, and absolute risk estimations in some cells, particularly in those groups of older adults with very high TC (> 7.8 mmol/L) and SBP, could be less accurate because of this fact and the lower number of individuals.

The study has several strengths. The sample size was large and recruited from different geographical areas of Spain (northern, central, and southern areas), and it covers a wide age range, including a large proportion of elderly people (> 3000, 25.4% of the total sample) and also people with DM. Almost half of participants were under pharmacological risk factor management (antihypertensive or lipid lowering drugs) at baseline, representing the current situation of CVD risk factor treatment at the population level. The ERICE estimates the total CVD risk (CHD and stroke), and also includes DM as a risk factor along with age, smoking, SBP, and TC. The availability of information on cardiovascular risk factor treatment,

particularly antihypertensive treatment, is another strength of this study, along with additional information useful for clinicians to adjust the estimated cardiovascular risk in those patients already under antihypertensive treatment.

The pooled ERICE cohort provides a new prospective analysis on the association between total CVD and several risk factors in Spain, a European country with a low incidence of CVD. The ERICE score allows the direct estimation of total CVD risk in Spain based on the risk estimation in the Spanish population, rather than being based on foreign scores calibrated for the low-risk European population. Such extrapolations may vary widely when a risk estimation formula is applied to a different population, and may not work properly.

Our results showed that the extent to which the effect of a specific risk factor, particularly TC, may need re-evaluation in the specific population to which it is going to be applied. It is expected that the internal validation of this risk score will be done in the near future. The external validation of the score in an independent Spanish cohort and the evaluation of its usefulness and impact compared with other existing scores, which deserved special attention in a recent issue of *Revista Española de Cardiología*,<sup>38 and 39</sup> are the next steps to approach. Finally, while this article was under review another function of global cardiovascular risk was published that included the population aged 35 to 79 years.<sup>40</sup>

## Conclusions

Age was the strongest risk factor for CVD in both sexes, as was well known. In our study, high SBP was the strongest modifiable risk factor of CVD in men, followed by DM and smoking. In women, DM played a crucial role, followed by high SBP and smoking. The contribution of TC to the CVD risk was small in the Spanish population, and in both sexes when considering all age groups in this study. The ERICE offers a new CVD risk estimation system for the Spanish population derived, from the local and contemporary CVD risk factor assessment comprising several local cohort studies from different parts of the country. The ERICE score offers a direct estimation of the total CVD risk rather than specific outcomes such as CHD only, and highlights the importance of considering existing drug treatment for high cardiovascular risk factors, inclusion of elderly people and the diabetic status in the risk estimation. The ERICE score is a new, practical tool for clinicians in Spain to estimate the total CVD in their patients.

## Funding

This research was funded by the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, grants G03/065 and PI05/1464; and by RECAVA (Red Temática de Investigación Cooperativa en Enfermedades Cardiovasculares), grant RD06/0014/0015.

## Conflicts of interest

None declared.

## Acknowledgments

To Rosario Madero from *Unidad de Bioestadística, IdiPAZ (Instituto de Investigación Sanitaria del Hospital Universitario La Paz), Hospital Universitario La Paz, Madrid* and to Nuria Soriano from *Centre d'Atenció Primària Sardenya, Barcelona* for statistical assistance; to Margarita Alonso Arroyo from IdiPAZ, Madrid and Teresa R. Pérez Castro from *Instituto Universitario de Ciencias de la Salud, Universidad de A Coruña* for data management. To Ana Isabel Ortega for editorial assistance.

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