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CALIBRATION AND DISCRIMINATION OF THE SCORE (SYSTEMATIC CORONARY RISK EVALUATION) MODEL FOR LOW-RISK COUNTRIES AND THE NEW RISK EQUATION OF THE US AMERICAN COLLEGE OF CARDIOLOGY (ACC) / AMERICAN HEART ASSOCIATION (AHA)

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1. Summary

Objective

The main objective of this study was to perform an independent external validation of the SCORE (Systematic COronary Risk Evaluation) model for low-risk countries, as well as for the new risk equation of ACC / AHA in asymptomatic individuals (primary prevention).

Design

Cross-sectional study of a nationwide cohort of a working population that included a personal interview as well as laboratory analysis.

Participants

All workers without a history of previous cardiovascular disease who attended a clinical examination between April 2006 and December 2007 were included.

Outcomes

New cardiovascular events (fatal and non-fatal) that occurred during follow-up period.

Statistical analysis

The cardiovascular risk for each participant was calculated using the risk equations of the SCORE model and the ACC / AHA and the risk obtained was compared with the actual morbidity and mortality (only for SCORE) registered among the participants. The predictive capacity of both cardiovascular risk models in our population was evaluated in terms of calibration and discrimination. The concordance between the events predicted by each of the cardiovascular risk models and the actual events recorded was assessed, stratified by risk deciles, by means of the goodness-of-fit test of Hosmer-Lemeshow Chi-Square, in the version of D'Agostino-Nam for survival data. The discrimination of the models was evaluated graphically through the ROC curves and by calculating the Harrell C statistic. The sensitivity, specificity, likelihood ratio and Youden index were calculated for the recommended cut-off points and the cardiovascular risk thresholds from which pharmacological treatment is recommended.

2. Results

244,236 subjects between 40 and 65 years of age participated in the study. 24.5% of the participants were women and the average age of the participants was 48.10 years (SD 6.26). 42.72% of the subjects were smokers at the time of the interview and 27.92% consumed alcohol on a regular basis.

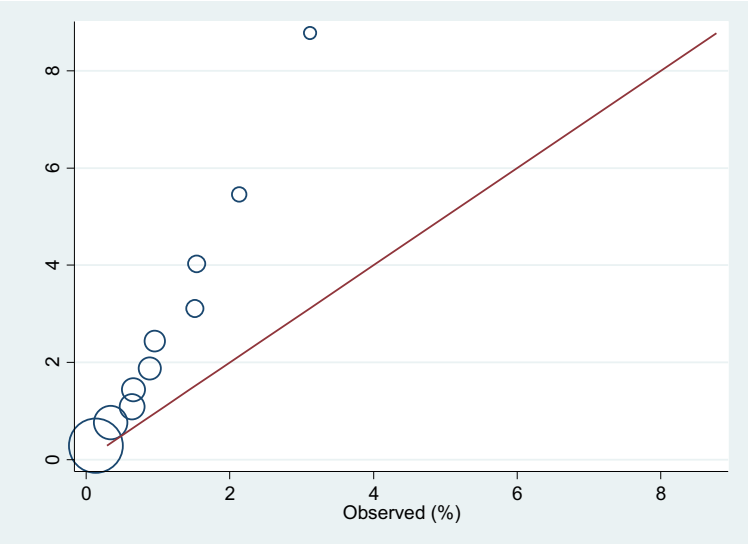
Table 1. Baseline characteristics of participants by sex.

		Men (n=184,380)	Women (n=59,856)
Age, mean (SD)		48.42 (6.38)	47.10 (5.75)
Tobacco n (%)	Non-smoker	53,753 (29.15%)	27,381 (45.74%)
Ex-smoker ≥1 year		42,476 (23.04%)	9,709 (16.22%)
Ex-smoker < 1 year		5,197 (2.82%)	1,388 (2.32%)
Smoker		82,954 (44.99%)	21,378 (35.72%)
Alcohol intake, n(%)	Daily	63,104 (34.22%)	5,094 (8.51%)
Work activity, n (%)	Not manual	46,442 (25.19%)	28,941 (48.35%)
Manual		137,023 (74.32%)	30,590 (51.11%)
n/a		915 (0.50%)	325 (0.54%)
BMI (kg/m^2), mean (SD) [n]		27.61 (3.97) [n=182,733]	25.53 (4.47) [n=58,993]
Total cholesterol (mg/dl), mean (SD) [n]		214.46 (37.38) [n=179,099]	208.48 (35.09) [n=57,839]
LDL- cholesterol (mg/dl), mean (SD) [n]		136.18 (33.36) [n=169,123]	129.41 (31.52) [n=55,603]
HDL-cholesterol (mg/dl), mean (SD) [n]		51.42 (12.51) [n=171,908]	61.86 (13.54) [n=55,633]
Triglycerides (mg/dl), mean (SD) [n]		139.09 (100.18) [n=177,484]	87.21 (49.08) [n=57,331]
SBP (mmHg), mean (SD) [n]		134.39 (17.52) [n=183,302]	123.42 (17.08) [n=59,494]
DBP (mmHg), mean (SD) [n]		81.84 (10.87) [n=183,284]	76,34 (10.55) [n=59,495]
Antihypertensive treatment, n (%)		15,595 (8.46%)	3,573 (5.97%)
DM 2, n (%)		5,345 (2.90%)	643 (1.07%)

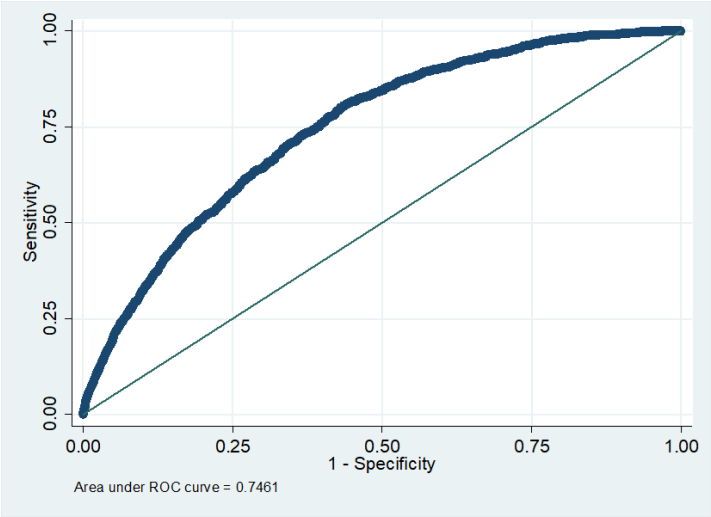
The SCORE risk was estimated in 228,986 (93.76%) of the participants, 6,917 (2.83%) of the subjects were excluded because they had a diagnosis of diabetes and the rest (3.41%) due to having SBP values and / or of total cholesterol outside the range required by the calculator. The risk according to the ACC / AHA equation was estimated in 232,606 participants (95.24%), 9,965 (4.08%) of the subjects were excluded because they were receiving lipid lowering treatment at the time of the interview, and the rest (0.68%) for presenting extreme values of PAS and / or total cholesterol and / or HDL cholesterol.

Cardiovascular risk according to SCORE calculator for low risk countries

The average risk according to SCORE was 1.70 (SD 1.81) for men and 0.37 (SD 0.53) for women. 5.17% of men and 0.07% of women had a risk between 5% and 9%, and only 0.62% of men had a risk equal to or greater than 10%. The average follow-up time was 9.81 years and during that period a total of 1,177 events (0.51%) of those considered in the SCORE calculator were recorded, 1,113 (0.64%) in men and 64 in women (0.11%); 59.64% of the events were classified according to the ICD-10 classification in groups I20-I25 (Ischemic heart disease). Most of the sample is concentrated in the first risk deciles and there is a systematic overestimation of the risk of the estimated values with respect to the values observed in all the risk deciles, registering overestimation ratios of between 1.72 (decile 3) to 2.81 (decile 10), resulting statistically significant with the Nam-D'Agostino test (p <0.001).



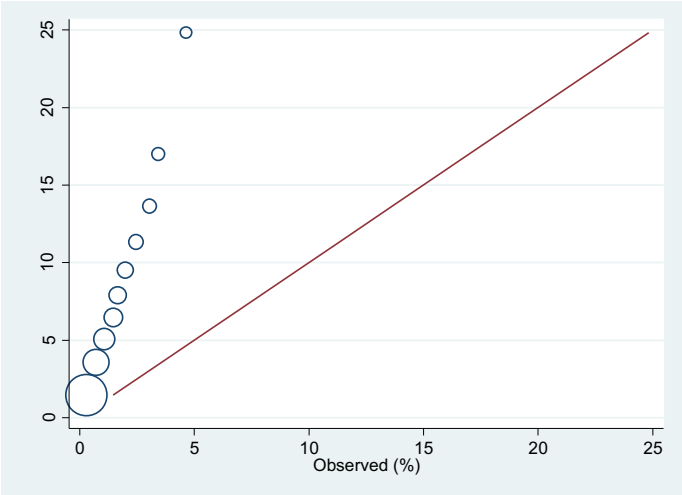
The Harrell statistic C was 0.746 (95% CI 0.733-0.759).



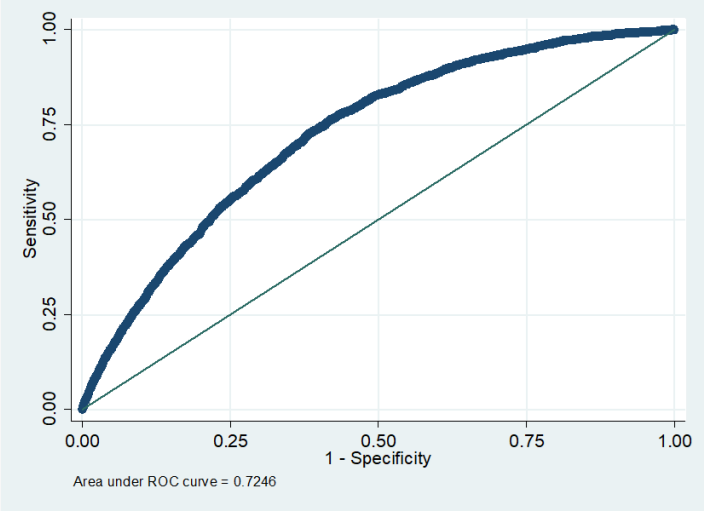
The calculated Youden index was 0.370, identifying as an empirical point of optimal cut the value 0.95%, in which the sensitivity would be 80%, the specificity 57% and the area under the ROC curve 0.69. When evaluating the sensitivity and specificity using the 5% cut-off point (threshold from which the high risk of cardiovascular mortality in the next 10 years is considered according to SCORE) the sensitivity of the model turns out to be 17.59% (CI95 % 15.52% - 19.87%) and the specificity 95.68% (95% CI 95.59% - 95.76%).

Cardiovascular risk according to ACC / AHA calculator

The average risk according to the PCE was 6.98 (SD 5.66) for men and 1.97 (SD 1.96) for women. 18.61% of men and 4.77% of women had a risk to the limit (5% -7.5%), 32.08% of men and 2.10% of women presented an intermediate risk (7.5% -20%) and 3.34% of men and 0.03% of women presented a risk equal to or greater than 20%. The average follow-up time was 10.77 years and during that period there were a total of 2,330 events (1.00%) of those considered in the PCE, 2,170 (1.24%) in men and 160 in women (0.28%); 70.81% of the events were due to ischemic heart disease. In the calibration by risk deciles, the first risk deciles concentrate the weight of most of the sample. The systematic overestimation of the risk of the estimated values with respect to the observed values was recorded in all risk deciles, with ratios ranging from 4.35 (decile 4) to 5.36 (decile 10), resulting statistically significant with the Nam test - D'Agostino ($p < 0.001$).



The Harrell C statistic was 0.725 (95% CI 0.715 - 0.734



The calculated Youden index was 0.344, proposing as an empirical point of optimal cut the value 4.99%, in which the sensitivity and specificity of the calculator would be 76% and 58%, respectively, and the area under the ROC curve of 0.67.

When evaluating the sensitivity and specificity using the 20% cut-off point, the sensitivity of the model turns out to be 9.06% (95% CI 7.96% - 10.29%) and the specificity 97.55% (95% CI 97.48% - 97.61%). Using the old cut-off point of 7.5%, the sensitivity of the calculator was 57.2% (95% CI 55.19% - 59.21%) and the specificity 73.2% (95% CI 72, 98% - 73.34%). Among individuals who suffered an event, 48.15% of them fell from the original risk category with the new cut-off point (NRI events = -0.482) and among individuals without an event, 24.38% also fell from

the original risk category (NRI events = 0.244), the global NRI was -0.2377, and the global NRI weighted by the prevalence of events was 0.365.

Comparison of the validity of calculators

The SCORE equation obtained a Brier index of 0.0053, Harrel E_{max} indices of 0.163 and E_{avg} of 0.009, while the PCE obtained a Brier index of 0.0142, E_{max} of 0.621 and E_{avg} of 0.047.

3. Clinical relevance and possible future implications

Currently, the SCORE risk tables for low-risk countries or REGICOR (calibration of the Framingham equation for Spain) are the tools most often used. The AHA / ACC tables for the calculation of the ASCVD risk were developed in the United States, and have also been also widely distributed. The results of the validation of our study demonstrate that the SCORE for low-risk countries and the ASCVD systematically overestimate the risk of our patients, so its use implies labeling high-risk patients when in fact they are not. This is relevant from a clinical point of view because it can lead to a more aggressive action on these patients both from a non-pharmacological and pharmacological point of view (with lipid-lowering, antihypertensive or antiplatelet drugs).Model discrimination is acceptable, but this was an expected result, because discrimination is rarely affected. However, the result of the validation obtained from the SCORE adjusting for morbidity is interesting, since in this case the calibration improves notably especially for individuals of low-moderate risk, although it is also true that the discrimination appears slightly reduced when compared with SCORE model of mortality only. The clinical implication of this result is that it is better to use the SCORE table adjusted for morbidity (multiplying the risk calculated for mortality by 3 in men and by 4 in women) than the SCORE tables that are used today. Thus, we would consider that a patient is at high risk if their risk is 15% or higher in the next ten years using the morbidity adjustment. These results should be taken into account in the new clinical practice guidelines for cardiovascular prevention, and we make the explicit recommendation that if SCORE is used, it is better to use the one adjusted for morbidity.

4. Scientific bibliography generated

Moral I, Brotons C, Fernández D, Puig M, Calvo E, Martínez P, Catalina C, Quevedo LJ. External validation of the European and American equations for the calculation of cardiovascular risk in the Spanish working population. (sent to the Spanish Journal of Cardiology on February 20, 2020, awaiting response).