

External Validation of Cardiovascular Risk Scores in the Southern Cone of Latin America: Which Predicts Better?

Validación externa de ecuaciones de riesgo cardiovascular en el Cono Sur de Latinoamérica: ¿cuál predice mejor?

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ABSTRACT

Background: Inaccurate estimates of demographic cardiovascular risk may lead to an inadequate management of preventive medical interventions such as the use of statins.

Objectives: The aim of this study was to evaluate the external validity of cardiovascular risk equations in the general population of the Southern Cone of Latin America.

Methods: Equations including variables evaluated in the CESCAS cohort study and that estimate overall cardiovascular mortality (CUORE, Framingham, Globorisk and Pooled Cohort Studies) were assessed. For each equation, an independent analysis was performed taking into account the cardiovascular events originally considered. Discrimination of each equation was evaluated through C-statistic and Harrell's C-index. To assess calibration, a graph was built for each equation with the proportion of observed events vs. the proportion of estimated events by risk quintiles and the β slope of the resulting linear regression was calculated. Sensitivity and specificity were determined for the detection of people at high cardiovascular risk.

Results: The median follow-up time of the cohort at the time of the analysis was 2.2 years, with an interquartile range of 1.9 to 2.8 years. Sixty cardiovascular events were incorporated into the analysis. All C-statistic and Harrell's C index values were greater than 0.7. The value of the β slope farthest from 1 was that of the Pooled Cohort Studies score.

Conclusions: Although the external validation parameters evaluated were similar, CUORE, Globorisk and the Framingham equations showed the best global performance for cardiovascular risk estimation in our population.

Key words: Cardiovascular disease - Risk factors, risk assessment, prevention.

RESUMEN

Introducción: La estimación inexacta del riesgo cardiovascular poblacional puede llevar a un manejo inadecuado de las intervenciones médicas preventivas, como, por ejemplo, el uso de estatinas.

Objetivo: Evaluar la validez externa de ecuaciones de predicción de riesgo cardiovascular en población general del Cono Sur de Latinoamérica.

Material y métodos: Se evaluaron ecuaciones que incluyen variables evaluadas en el estudio CESCAS y que predicen tanto morbilidad como mortalidad cardiovascular global (CUORE, Framingham, Globorisk y Pooled Cohort Studies Equations). Para cada ecuación se realizó un análisis independiente en el que se tuvieron en cuenta los eventos cardiovasculares relevados. Se evaluó la discriminación de cada ecuación a través del cálculo del estadístico-C y el índice Harrell C. Para evaluar la calibración se graficó la proporción de riesgos observados vs. estimados por quintiles de riesgo para cada ecuación y se calculó la pendiente β de regresión lineal para las estimaciones. Se calculó sensibilidad y especificidad para la detección de personas con elevado riesgo cardiovascular.

Resultados: La mediana del tiempo de seguimiento de la cohorte al momento del análisis es de 2,2 años, con un rango intercuartilo de 1,9 a 2,8 años. Se incorporaron a los análisis 60 eventos cardiovasculares. Todos los valores de estadístico-C y del índice de Harrell fueron superiores a 0,7. El valor de la pendiente β más alejado de 1 fue el de Pooled Cohort Studies Equations.

Conclusiones: Si bien los parámetros de validación externa evaluados fueron similares, CUORE, Globorisk y el índice de Framingham fueron las ecuaciones con mejores indicadores globales de predicción de riesgo cardiovascular.

Palabras claves: Enfermedad cardiovascular - Factores de riesgo - Evaluación del riesgo - Prevención

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Abbreviations

CV Cardiovascular	CVR Cardiovascular risk
CVD Cardiovascular disease	

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death both in developed and in developing countries. Approximately 80% of deaths of CV origin occur in low and middle income countries (1, 2) The INTERHEART study showed that nine measurable and potentially modifiable risk factors are responsible for 90% of acute myocardial infarctions. (3) Most of these CV risk (CVR) factors also represent the main causes of disease burden worldwide. (4) It is critical for developing countries to improve their ability to detect individuals at high CVR in order to benefit from more intense medical interventions.

In recent years, the estimation of CVR has assumed a central role in CV primary prevention, and research in the field of risk prediction has become subject of profound study. (5) The estimation of future CVR not only aids global clinical management as basis for individual therapeutic decision-making but also as a tool to evaluate the risk profile at the population level. (6) Decisions in CV prevention should be adopted after an adequate estimation of CVR; for example, medical treatment with statins in individuals at high CVR. (7) In turn, the calculation of CVR is not only an essential support tool for clinical decision-making, but also aids with the communication and diffusion of information to patients. (5)

Cardiovascular risk prediction scores are practical, easy to use tools at the level of primary care. Most models of CVR prediction have been built in developed countries using databases with different socio-demographic, epidemiological and nutritional realities than those found in the South Cone of Latin America regions. (5) In this context, inaccurate risk prediction may lead to inadequate onset of medical interventions in individuals at lower real risk than that predicted by equations created in different populations. (8, 9)

The aim of this study was thus to evaluate the external validity (calibration, discrimination, sensitivity and specificity) of CVR prediction equations built in developed countries, in the first follow-up data of the Center of Excellence in Cardiovascular Health for South America (CESCAS) cohort, a representative general population sample of four cities in the South Cone of Latin America (Argentina, Chile and Uruguay). To our knowledge, this is the first study that evaluates and compares different CVR prediction equations in populations belonging to the South Cone of Latin America. (9-11).

METHODS

Selected prediction equations

The selection of CVR prediction equations was based on mod-

els presented in the 2016 European guidelines on CVD prevention in clinical practice. (12) The equations incorporated for the analysis were selected following two steps: Firstly, prediction models whose variables had all been evaluated in the Southern Cone of Latin America CESCAS cohort were included and then, equations predicting only CV mortality or coronary events were finally excluded. The models evaluated were: ASSIGN-SCORE, (13) QRISK1 (14) & QRISK2 (15), SCORE, (16) PROCAM, (17) Pooled Cohort Studies Equations, (18) Framingham, (19) CUORE (20) and Globorisk. (21). Equations selected for evaluation corresponded to the last four risk models. Figure 1 depicts the selection process and Table 1 describes the final events predicted by these equations, the variables included in the models and the age ranges evaluated.

The CESCAS cohort

The details of the analysis and sampling method of the CESCAS cohort study have been previously published. (22-23). Essentially, CESCAS is a prospective cohort study including

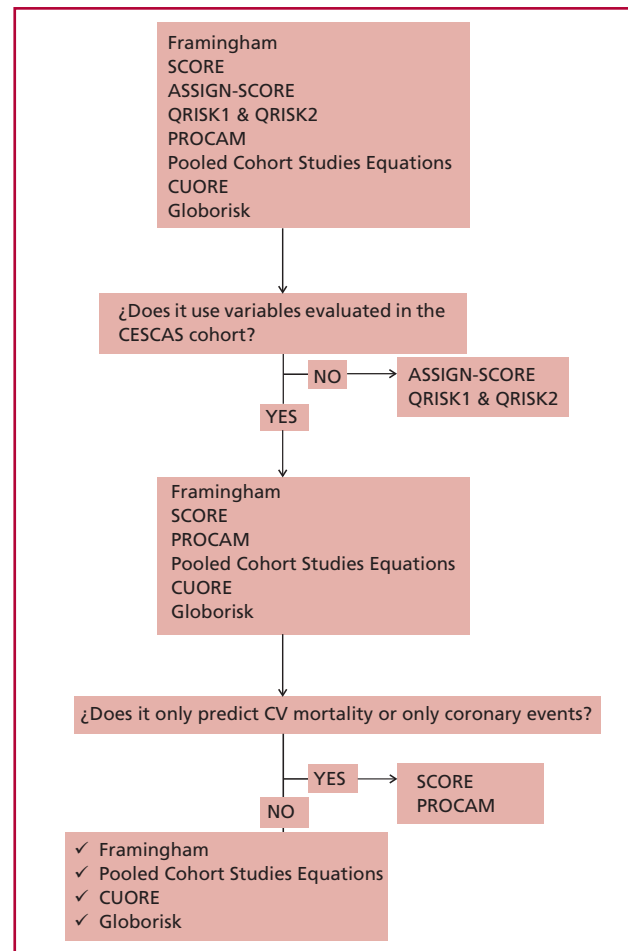


Fig. 1. Selection process of cardiovascular risk equations

Table 1. Characteristics of the models evaluated[‡]

	CUORE	Framingham	Globorisk	Pooled Cohort Studies Equations
Variables included in the models	Sex	Sex	Sex	Sex
	Age	Age	Age	Age
	Total cholesterol	Total cholesterol	Total cholesterol	Total cholesterol
	HDL-C	HDL-C	-----	HDL-C
	SMK	SMK	SMK	SMK
	SBP	SBP	SBP	SBP
	-----	DBT	DBT	DBT
	Antihypertensive treatment	Antihypertensive treatment	-----	Antihypertensive treatment
Age range	35-69	35-69	35-69	35-69

[‡] SMK: Smoking. SBP: Systolic blood pressure. DBT: Diabetes. HDL-C: HDL-cholesterol

7,524 adults (3,165 men and 4,359 women) from 35 to 74 years of age, recruited between December 2010 and December 2012. The sample originates from polystage sampling representative of the general population of four cities of the Southern Cone of Latin America: Bariloche and Marcos Paz (Argentina), Temuco (Chile) and Canelones (Uruguay). The global response rate was 73.4% and was similar in men and women across cities.

Study data were collected during a home visit and in another visit to a medical center. Socio-demographic information (age, sex, education and occupation) was obtained during the home survey. Anthropometric measurements were obtained by certified, trained staff using standardized protocols and techniques. Blood pressure was measured with the participant seated after a 5-minute rest, using a standard mercury or aneroid sphygmomanometer, and the average of three readings was considered for the analysis. Body weight, height and waist circumference were measured twice during the evaluation, and their average was used in all the analyses.

A fasting blood sample was withdrawn to assess lipoproteins, creatinine and blood sugar levels. The fasting interval was verified before blood withdrawal and no blood sample was taken if fasting was below 10 hours. Standard methods were used to determine blood glucose, total cholesterol, HDL-cholesterol, triglycerides and creatinine. LDL-cholesterol concentration was calculated using Friedewald's equation when triglycerides were <400mg/dL. (24) Diabetes was defined as blood sugar levels ≥ 126 mg/dL and/or self-reported history of diabetes and/or its current treatment with insulin or oral anticoagulants.

Cardiovascular events (angina, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, coronary artery, carotid or peripheral revascularization procedure, heart failure and sudden death) in this first follow-up evaluation were confirmed by a specialist in internal medicine or a cardiologist after verifying the event-specific record. Of importance, the CESCAS cohort did not reveal intermittent claudication, one of the Framingham equation endpoints.

Statistical analysis: external validation of the models

The regression coefficients of the original publications were obtained for each selected model. Together with these coefficients, all the equations were recalibrated to the CESCAS population with the following exponential equation: (19)

$$\hat{p} = 1 - S_0(t)^{\exp(\sum_{i=1}^p \beta_i X_i - \sum_{i=1}^p \beta_i \bar{X}_i)}$$

where S₀ (t) is survival at the specific follow-up time; β_i are the estimated coefficients of regression (Log hazard ratio); X_i is the specific value of each risk factor considered for the equation; \bar{X}_i refers to the mean value of each risk factor in the CESCAS population at baseline and p corresponds to the number of risk factors for each equation.

A different “endpoint” variable for each equation was created in the database (Table1), specifically including the events for which they were designed as prediction tools.

The discrimination of each equation was assessed through the calculation of the C-statistic (Area under the ROC curve, AUROC) and Harrell's C-index. The C-statistic is the most commonly used measurement for the discrimination of CV prediction models. It reflects the ability of this index to discriminate between individuals presenting or not events. Namely, it expresses the probability that a randomly selected case (event) has a risk score above a randomly selected non-case (without event). (5) Harrell's C-index is another similar statistical tool to compare the discrimination of a model, but allows the addition of follow-up time, which measures its capacity to assign high risk to individuals with short time to the event. (25, 26) Calibration was analyzed comparing predicted and observed events per risk quintile. In addition, the β slope of the linear regression estimates was calculated, where values close to 1 indicate better model calibration.

For the calculation of sensitivity and specificity, the American guidelines suggest a cut-off point of 7.5% risk at 10 years. Since the follow-up time of the present cohort is lower, the cut-off point was estimated as 3% risk. This adaptation was performed using the following formula: 1 - Exp (-1*average annual incidence of events*follow-up time for the 95% cohort percentile). Sensitivity was calculated as true positives (TP)/(TP + false negatives) *100. Specificity was calculated as true negatives (TN)/TN + false positives) *100.

Ethical considerations

This study was performed following data protection rights guidelines of people who voluntarily participated in the study. All CESCAS cohort participants signed an informed consent including the authorization of data use for secondary analysis. Cohort protocol was approved by the Ethics

Committees of all the centers participating in Argentina, Chile and Uruguay.

RESULTS

Follow-up of the CESCAS cohort

After the exclusion of participants with history of CVD at baseline cohort evaluation, and cases without available complete baseline biochemical tests, 6,364 participants were included in the study. At the time of analysis of the present database, median follow-up was 2.2 years, interquartile range 1.9-2.8 years. A total of 60 primary CV events occurred during that interval: 21 anginas and acute myocardial infarctions, 15 strokes, 10 heart failures, 2 coronary artery revascularization procedures and 12 CV deaths.

External validation parameters

Table 2 presents the discrimination parameters alphabetically ordered. Table 3 summarizes the calibration

parameters analyzed and Table 4 shows the sensitivity and specificity values for the detection of individuals with elevated CVR.

DISCUSSION

The study assessed external validation parameters of equations estimating CVR in a Southern Cone of Latin America cohort. Even though current follow-up data of the CESCAS cohort did not provide significant differences among selected equations, we should point out that CUORE, Framingham and Globorisk scores had the best prediction parameters in this population.

According to the literature, ROC curves rarely exceed 0.8 values (27) in this type of validation analyses. In this study, all the curves in the CESCAS cohort were above 0.7, with Globorisk and CUORE presenting the highest C-statistics. Moreover, Harrell's C-index was similar among the different equations. Assessment of the degree of agreement between observed and pre-

Table 2. Discrimination parameters evaluated

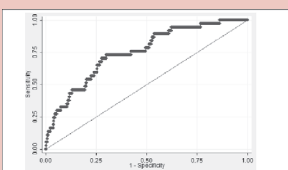
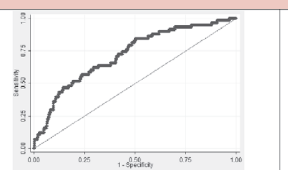
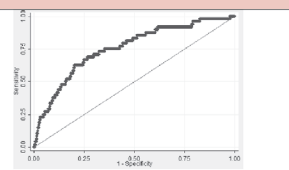
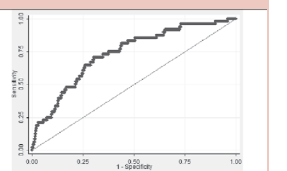
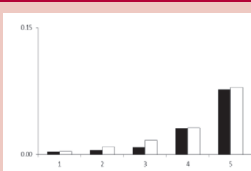
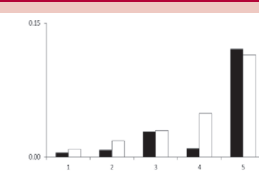
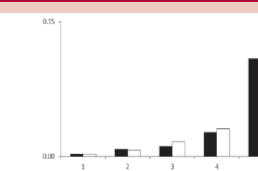
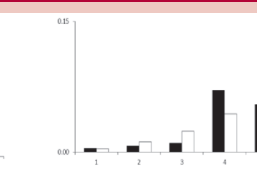
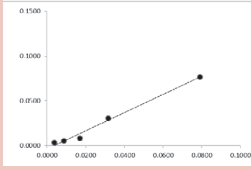
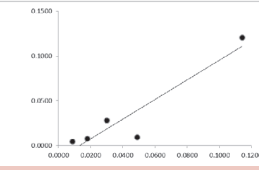
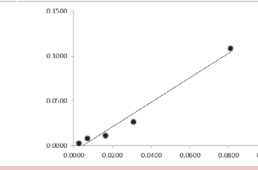
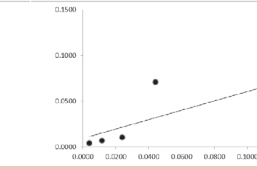
Equatio	CUORE	Framingham	Globorisk	Pooled Cohort Studies Equations
ROC curve				
C-statistic	0.751	0.719	0.753	0.736
Harrell's C index	0.752	0.722	0.736	0.743

Table 3. Calibration parameters evaluated

Equatio	CUORE	Framingham	Globorisk	Pooled Cohort Studies Equations
Observed (■) vs. estimated (□) risk per risk quintiles				
Linear regression of observed vs. estimated risk				
β slope	$y = 1.012x - 0.0036$	$y = 1.0956x - 0.014$	$y = 1.3718x - 0.0066$	$y = 0.5103x + 0.0095$

	CUORE	Framingham	Globorisk	Pooled Cohort Equations
Sensitivity	73%	81%	75%	75%
Specificity	69%	51%	60%	58%

Table 4. Sensitivity and specificity for the identification of high cardiovascular risk

dicted model values (calibration) showed that CU-ORE, Globorisk and Framingham were the equations with highest accordance in the comparison per risk quintiles and with β coefficient closer to 1, whereas the AHA Pooled Cohort Studies Equations showed model instability in the higher risk quintiles with β coefficient farther from 1. The four equations showed comparable sensitivity and specificity to detect individuals at elevated CV risk, the Framingham equation evidencing the highest value for sensitivity and CU-ORE for specificity.

Certain observations and limitations should be mentioned about the conclusions of this study: 1) the current follow-up time of the CESCAS cohort does not allow a long-term prediction analysis; however, all the analyses performed in the study were adjusted to survival according to the follow-up time; 2) future analyses will have a greater number of CV events, allowing the incorporation of equations evaluating exclusively CV mortality such as the SCORE model; and 3) intermittent claudication cases were not considered for the evaluation of the Framingham equation, as they were not recorded in the cohort.

Among the strengths of this study, we should first mention that, to our understanding, no other external validation analysis of CVR equations has been previously published in the general population of the Southern Cone of Latin America; second, calibration of each equation for baseline risk of the CESCAS cohort population was performed using prevalent risk factor data, which would not have been possible without individual population data for a more accurate adaptation of the model to the population under the study (27), and; third, independent analyses were performed for each equation taking into account the final events they evaluate and the age range for which they were designed.

Current work in the CESCAS cohort will not only increase the complexity of external validation analyses of the equations developed, but will also allow the construction of a proper regional prediction model and the evaluation of other types of non-conventional prediction variables as inflammation or atherogenic biomarkers (PCR, lipoprotein A).

CONCLUSIONS

Risk prediction equations evaluated in the study showed similar risk prediction parameters and CU-ORE, Framingham and Globorisk equations presented the best parameters. These results represent a first approximation for the selection of the most adequate prediction model for our population. Future cut-off points of CESCAS cohort with longer follow-up and higher number of events will improve the CVR classification at the population level based upon the evidence resulting from data of our region.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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