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Cardiovascular Risk Prediction Models in People Living with HIV in Colombia

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ABSTRACT

Background: People living with HIV are at increased risk of cardiovascular disease. Cardiovascular risk (CVR) prediction scores are powerful tools for individualized assessment that inform decision-making about follow-up frequency, hypolipemiant treatment intensification, and choice antiretroviral therapy. **Objectives:** The objectives of the study were to evaluate the performance of multiple cardiovascular assessment scores in predicting major adverse cardiovascular events (MACE) at 5 and 10 years. Framingham (2004, 2008, and Colombia-adjusted), SCORE, PROCAM, ASCVD, and D:A:D scores were included in the analysis. **Methods:** Data were obtained from a medical registry of adults living with HIV attended by a teaching hospital in Colombia. All patients with complete information necessary for risk score calculations and determination of MACE at 5 and 10 years were included in the study. Receiver operating characteristic curves (ROC) were generated using calculations with all the aforementioned models for every individual. Differences between curves were compared with DeLong's test. **Results:** A total of 808 patients were included in the analysis. Mean age was 35 years, and 12% were female. The majority of subjects had low and very low CVR. Eight MACE occurred during follow-up. Area under ROC curves were: Framingham (0.90), Framingham ATP3 (0.92), Framingham calibrated for Colombia (0.90), SCORE (0.92), PROCAM (0.92), ASCVD (0.89), and D:A:D (0.92), with no statistically significant differences. **Conclusions:** The evaluated scores had an acceptable performance for HIV-infected patients in the studied cohort, especially for those in low and very low risk categories. (REV INVEST CLIN. 2022;74(1):23-30)

Keywords: Risk. HIV. Cardiovascular disease. Prediction. Score. Latin-American.

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INTRODUCTION

Individuals infected with HIV have a 1.5-times higher risk of cardiovascular disease (CVD) compared with non-infected individuals, after controlling for traditional cardiovascular risk (CVR) factors[1-6]. The prevalence of these traditional risk factors is higher in the HIV+ population than in the general population. However, other independent risk factors for CVD have been described that are specific for HIV individuals, such as low CD4+ T lymphocyte count and use of certain antiretroviral agents[3].

CVR prediction models are mathematical functions that allow to estimate the incidence of major cardiovascular events (major adverse cardiovascular events [MACE], i.e., cardiovascular death [CVD], stroke [CVA], coronary artery disease [CAD], and peripheral artery disease). They combine risk factors such as age, sex, smoking, lipid fraction blood levels, blood pressure, and among others, into prespecified equations that ponder the weight of each item in the probability of MACE occurrence. These equations are used for the prediction of CVR of an individual who, in turn, supports decision-making on lipid fraction level goals, hypolipemiant treatment, use of other therapies (e.g., antiplatelets), intensity of follow-up, and modification of antiretroviral treatment (HAART).

Several risk prediction models have been developed; they assess the probability of MACE at 5 and 10 years in the general population[7-14] and others that include cohorts from some Latin American countries[9,15,16]. However, few of them have been evaluated in HIV-positive populations[17-19]. Only the Data Collection on Adverse Events of Anti-HIV Drugs Study (D:A:D)[18] includes variables that are unique to this population, such as log of CD4+ T lymphocyte count and accrual exposure to protease inhibitors, nucleoside reverse transcriptase inhibitors, and abacavir.

Information about risk prediction models in HIV patients in Colombia and Latin America is extremely limited, and even worldwide information is scarce. The objective of this study is to evaluate the performance of D:A:D score[18] and other five widely known equations, in predicting MACE in a population of HIV-infected adults in Colombia.

METHODS

Hospital Universitario San Ignacio (HUSI) keeps a medical registry of its population with HIV since 2004. It collects information on socio-demographic data, immunovirological status, hematology, liver and kidney function tests, plasma lipidic fractions, HAART, comorbidities, and among other. Data were gathered from follow-up visits scheduled every 6-12 months in accordance with practice guidelines[20-22]. For this study, subjects were included if they were followed-up for at least 5 years. It was also required that information necessary for calculation of risk scores and incidence of MACE at 5 and 10 years was available. This study was approved by the institutional review board of HUSI and Pontificia Universidad Javeriana (code: FM-CIE-0619-18). As this study used only information from routine medical care, and data were anonymized, informed consent was waived in accordance with international regulations and Colombian law.

Cardiovascular risk prediction models

The following models were included in the study: Framingham (in its 2004, 2008, and Colombia adjusted versions), the European Systematic Coronary Risk Evaluation (SCORE), the Prospective Cardiovascular Münster Study (PROCAM), the pooled cohort equations of the American Heart Society/American College of Cardiology (PCE), and the D:A:D score[2,11,13,14,18,23]. Other CVR prediction equations were not included, due to the lack of information available for their calculation[9,15,16].

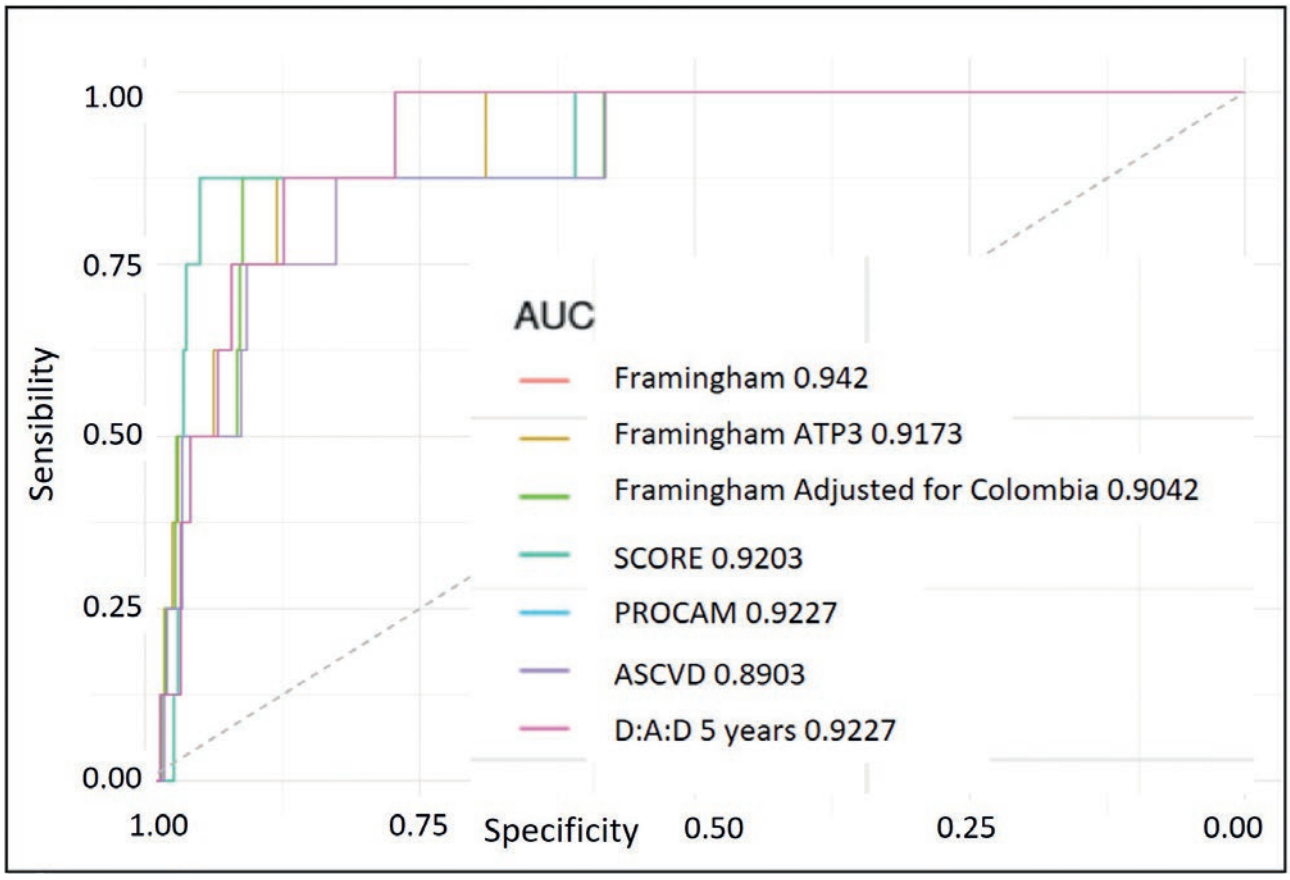
Variables and outcomes

Information necessary for the calculation of all risk scores was obtained from electronic health records (EHR). This included history of tobacco use, diabetes mellitus, CVD, hypertension, family history, and among others. Values of lipidic fractions were drawn from the results of the first set of laboratory tests after admittance to the program. To determine vital status and occurrence of MACE at 5 and 10 years, EHR were thoroughly reviewed.

Statistical analysis

Categorical variables are presented with their frequencies and proportions. Quantitative variables are

Figure 1. Receiver operating characteristic curves.



summarized with mean, median, and interquartile range. CVR was established at the beginning of follow-up for everyone using all the aforementioned models. Receiver operating characteristic curves (ROC), area under ROC curve (AUC), and C-statistic were then calculated and compared using DeLong's test. Data were analyzed using RStudio Team (2020) - ROCS R Package. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.

RESULTS

A total of 1,003 patients met the inclusion criteria; mean age was 35 years, and 12% were women. Five percent were either diabetic or hypertensive and 29% were smokers. Table 1 summarizes baseline characteristics of total cohort. Of this group, 195 patients (19.4% of total cohort) were excluded due to lack of information on MACE at 5-10 years, and the remaining 808 patients had their risk calculated with all the models. Table 2 summarizes risk calculation for the whole cohort with each equation. Only eight patients presented MACE (< 1 %), two patients died due to CVD, four patients developed CAD, and two developed CVA.

After evaluating ROC curves (Fig. 1), all models presented an acceptable performance in predicting CVR in this sample, with an AUC > 0.89 and narrow confidence intervals. There were no statistically significant differences between these AUC.

DISCUSSION

Evaluation of CVR with validated models is essential when caring for adult patients. It predicts future incidence of MACE and helps establish recommendations on lifestyle modification, institution/intensification of treatment, and frequency of

Table 1. Baseline characteristics of the cohort

Variables	Women	Men		All	
	No MACE (n=121)	No MACE (n=874)	MACE (n=8)	No MACE (n=995)	MACE (n=8)
Age - years					
Mean (SD)	35.7 (11.2)	34.6 (9.98)	56.5 (0.707)	34.8 (10.1)	56.5 (0.707)
CD4 - cell/mm³					
Median [Min, Max]	279 [3.00, 1170]	292 [1.00, 1370]	222 [106, 338]	292 [1.00, 1370]	222 [106, 338]
Smoker					
Yes	105 (86.8%)	598 (68.4%)	1 (50.0%)	703 (70.7%)	4 (50.0%)
No	16 (13.2%)	276 (31.6%)	1 (50.0%)	292 (29.3%)	4 (50.0%)
TC - mg/dL					
Median [Min, Max]	177 [107, 275]	167 [70.2, 538]	173 [128, 217]	169 [70.2, 538]	173 [128, 217]
TG - mg/dL					
Median [Min, Max]	139 [41.4, 827]	139 [31.2, 2500]	196 [131, 262]	139 [31.2, 2500]	196 [131, 262]
HDL - mg/dL					
Median [Min, Max]	43.3 [21.6, 82.0]	34.4 [4.60, 76.0]	40.9 [30.1, 51.6]	35.0 [4.60, 82.0]	40.9 [30.1, 51.6]
SP - mmHg					
Mean (SD)	112 (13.5)	113 (11.4)	110 (14.1)	112 (11.6)	110 (14.1)
DP - mmHg					
Mean (SD)	71.1 (9.98)	71.9 (9.26)	65.0 (7.07)	71.8 (9.35)	65.0 (7.07)
Statin					
No	118 (97.5%)	851 (97.4%)	1 (50.0%)	969 (97.4%)	6 (80.0%)
Yes	3 (2.5%)	23 (2.6%)	1 (50.0%)	27 (2.6%)	2 (20.0%)
ASA					
No	119 (98.3%)	868 (99.3%)	1 (50.0%)	987 (99.2%)	4 (50.0%)
Yes	3 (1.7%)	8 (0.7%)	1 (50.0%)	8 (0.8%)	4 (50.0%)
Diabetes					
No	120 (99.2%)	860 (98.4%)	2 (100%)	980 (98.5%)	8 (100%)
Yes	1 (0.8%)	14 (1.6%)	0 (0%)	15 (1.5%)	0 (0%)

(Continues)

Table 1. Baseline characteristics of the cohort *(continued)*

Variables	Women	Men		All	
	No MACE (n=121)	No MACE (n=874)	MACE (n=8)	No MACE (n=995)	MACE (n=8)
BP					
No	114 (94.2%)	833 (95.3%)	0 (0%)	947 (95.2%)	0 (0%)
Yes	7 (5.8%)	41 (4.7%)	2 (100%)	48 (4.8%)	8 (100%)
Anti-HTA					
No	114 (94.2%)	836 (95.7%)	0 (0%)	950 (95.5%)	0 (0%)
Yes	7 (5.8%)	38 (4.3%)	2 (100%)	45 (4.5%)	8 (100%)

AntiHTA: antihypertensive drugs; ASA: acetyl salicylic acid; BP: blood pressure; TC: total cholesterol; DP: diastolic pressure; HDL: high-density lipoprotein; MACE: major adverse cardiovascular events; TG: triglycerides; SD: standard deviation; SP: systolic pressure.

follow-up. However, these models have limitations resulting from the differences (geographical, ethnical, and chronological) in the various derivation and validation cohorts that were used for their development. In spite of these limitations, numerous clinical practice guidelines on dyslipidemia and CVR agree in recommending the use of one of these equations to predict risk. Ideally, the choice of a scale over another should be based on adequate validation of reproducibility and performance in the specific population for which it is intended to be used.

There are no models developed specifically for the evaluation of CVR in Latin America and the Caribbean. Carrillo-Larco *et al.* found an acceptable performance for different CVR evaluation models in their systematic literature review, with some limitations derived from sample size and number of CVE during follow-up[24]. Others with some validation in Latin America, such as GLOBORISK and INTERHEARTRISK SCORE, and risk calculators from PAHO/WHO[9,15,16], were not analyzed because they were not used in the population object of this study, or because they did not have complete information for their estimation. They highlight that the models with best performance in Latin America are Framingham and ASCVD. Some studies with HIV populations have been reported from Brazil, although with small sample size and short follow-up[24-27].

To the best of our knowledge, this is so far the study of this nature with the largest sample size of HIV-infected individuals in Latin-America. We demonstrate a good performance in this population for the most frequently used equations in the region. The AUC values and narrow confidence intervals without statistically significant differences between models suggest that any of these equations may be used for this specific population.

Nevertheless, one limitation of our study is the fact that it was derived from a single center, with a small size compared with that of the derivation cohort of every equation. In addition, our cohort consisted mainly of young patients (mean age 35 years), with low and very low risk, which sets a limitation for the interpretation of results in patients with higher risk. However, the HIV+ population in Colombia is generally young[10]. The low incidence of MACE during follow-up may be explained by this young age and a low prevalence of the other traditional risk factors at baseline and to a good adherence to guidelines. However, the small number of outcomes makes the calculation of false-negatives and false-positives limited, thus the results are of very low external validity. Subgroup analysis was not performed given the low number of outcomes (MACE).

Another important consideration is that 19% of the cohort was excluded due to lack of information on

Table 2. Cardiovascular risk prediction

Cardiovascular risk prediction model %	Major adverse cardiovascular event		Total
	No	Yes	
Framingham			
Mean (SD)	2.16 (±4.99)	10.78 (±6.42)	2.25 (±5.07)
Median (Q1-Q3)	0.38 (0.06-1.81)	10.25 (7.01-14.25)	0.40 (0.06-1.86)
[Min-Max]	[0-61.31]	[0.79-20.76]	[0-61.31]
Framingham ATP3			
Mean (SD)	3.24 (±4.98)	11.41 (±5.92)	3.33 (±5.05)
Median (Q1-Q3)	1.89 (0.94-3.53)	11.15 (7.17-15.76)	1.90 (0.96-3.59)
[Min-Max]	[0.16-59.76]	[2.98-18.78]	[0.16-59.76]
Framingham for Colombia (Calculated risk × 0.75)			
Mean (SD)	1.62 (±3.74)	8.08 (±4.82)	1.68 (±3.81)
Median (Q1-Q3)	0.29 (0.05-1.36)	7.69 (5.25-10.69)	0.30 (0.05-1.39)
[Min-Max]	[0-45.98]	[0.59 - 15.57]	[0 - 45.98]
SCORE			
Mean (SD)	0.27 (±0.40)	1.16 (±0.41)	0.27 (±0.40)
Median (Q1-Q3)	0.07 (0.01-0.33)	1.31 (1.24 - 1.34)	0.07 (0.01 - 0.34)
[Min-Max]	[0-1.97]	[0.15-1.41]	[0-1.97]
PROCAM			
Mean (SD)	1.62 (±5.68)	7.17 (±6.55)	1.67 (±5.71)
Median (Q1-Q3)	0.37 (0.14-1.00)	5.30 (3.09-9.29)	0.37 (0.14-1.05)
[Min-Max]	[0-96.63]	[1.11-21.46]	[0-96.63]
ASCVD			
Mean (SD)	1.85 (±4.66)	6.17 (±4.10)	1.89 (±4.67)
Median (Q1-Q3)	0.92 (0.48-1.72)	5.66 (3.31-8.56)	0.94 (0.48-1.74)
[Min-Max]	[0.02-99.92]	[1.13-12.07]	[0.02-99.92]
D:A:D			
Mean (SD)	0.65 (±2.27)	2.87 (±2.62)	0.67 (±2.28)
Median (Q1-Q3)	0.15 (0.06-0.40)	2.12 (1.24-3.72)	0.15 (0.06-0.42)
[Min-Max]	[0-38.65]	[0.44-8.58]	[0-38.65]

Table 3. AUC and confidence intervals

CV Risk Scores	Lower limit	AUC	Upper limit
Framingham	0.81	0.90	1.00
Framingham ATP3	0.85	0.92	0.99
Framingham for Colombia	0.81	0.90	1.00
SCORE	0.83	0.92	1.00
PROCAM	0.87	0.92	0.97
ASCVD	0.80	0.89	0.99
DAD 5 years	0.87	0.92	0.97

MACE and vital status at 5 and 10 years. This population might have contributed with more events. Likewise, there may be a selection bias – the sample population had a very good adherence to treatment and received a strict follow-up – which may have improved cardiovascular outcomes in the short and long term. On the other hand, our study is innovative regarding its sample size and the population included, in comparison with the information thus far available, and therefore, does not allow fully generalizing them to other populations.

In conclusion, risk models evaluated in this study had an acceptable performance for the prediction of cardiovascular events in a particular Colombian HIV cohort, especially for low and very low risk individuals. However, the limitations of the study do not allow us to give a general recommendation for the Latin American population with HIV. Therefore, it may be advisable to evaluate the validation and performance of different CVR equations with multicenter studies and larger sample sizes. Perhaps selecting the model that requires fewer variables when evaluating patients with HIV in Colombia may be reasonable.

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