# Association between cardiovascular disease risk scores and subclinical atherosclerosis prevalence in non-elderly adult patients from Argentina

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## Abstract

The goal of our study was to use statistical analysis to try to associate

cardiovascular disease (CVD) risk scores and the observed prevalence of subclinical atherosclerosis (SA) in a non-elderly adult local population. An observational cross-sectional study was carried out (143 male and 131 female) on non-elderly adults (20–59 years). CVD risk scores included Framingham Risk Scores for 10-year hard (FRS 10 H), 30-year lipid hard or CVD (FRS 30 L H or FRS 30 L CVD), 30 year-body mass index hard or CVD (FRS 30 BMI H or FRS 30 BMI CVD) and Pooled Cohort Risk Equations for either 10 years (PCE 10) or lifetime (PCE LT). The Carotid Ultrasound (CU) study was performed and the Coronary Artery Calcium (CAC) score were obtained to assess SA. The Receiving Operating Characteristic (ROC) curve analysis followed by Youden's index was used to evaluate and adjust the stratification of CVD risk scores. SA was detected in 32.4% of individuals. The risk scores that showed the biggest areas under the ROC curve were FRS 30 L (H and CVD). When the cut-off values for these CVD risk scores were adjusted, the FRS 30 L H increased the negative predictive value for the low risk group from 87.7 to 97.0% and the FRS 30 L CVD increased the positive predictive values for the high risk group from 69.7 to 85.7%. The CVD risk stratification of non-elderly adults using FRS 30 L H and FRS 30 L CVD may be a useful tool for selecting candidate patients for diagnostic imaging studies that assess their SA prevalence.

## Keywords

Cardiovascular disease
Subclinical atherosclerosis
Framingham risk scores
Pooled cohort equations
Argentina

### Electronic supplementary material

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# Introduction

Atherosclerosis is a chronic inflammatory disease of the vascular wall, which is

mainly associated with cardiovascular disease (CVD) and constitutes the most frequent cause of death in Argentina [1, 2]. CVD is characterized by various events including acute myocardial infarction, angina pectoris, stroke, transient ischemic attack, peripheral artery disease and aortic disease [3]. Since atherosclerosis has a prolonged subclinical period, there is a great window of opportunity for preventive therapeutical and non-therapeutical interventions [3]. To assess adequately the risk of developing CVD to enable primary prevention strategies, different predictors of cardiovascular morbidity and mortality can be obtained by using the Framingham Risk Scores (FRS) or the latest *Pooled Cohort Atherosclerotic Cardiovascular Disease (ASCVD) Risk Equations* (PCE) [4, 5, 6]. However, the use of these predictors has some limitations [7], with probably the most important being that these risk scores need to be validated for each local population [8].

There are at least two imaging methods currently available to detect subclinical atherosclerosis (SA). One of these is to measure the increase in carotid intimal-media thickness (CIMT) in addition to searching for the presence of a carotid atherosclerotic plaque by carotid ultrasound (CU) [9, 10, 11]. Another method is to check for a positive coronary artery calcium (CAC) score, using a Cardiac Computed Tomography (Cardiac CT) [12, 13, 14]. Although the detection of SA by any of these methods constitutes an independent predictor of cardiovascular events and as such can be used as a valuable surrogate reference [9, 11, 14], the technical complexity and the high cost of these diagnostic tools require a careful selection of candidate patients. The goal of our study was to use statistical analysis to try to associate CVD risk scores to the observed prevalence of ~~subclinical atherosclerosis (SA)~~SA in a non-elderly adult local population, which would allow us to rationalize the use of CU and Cardiac CT images.

# Materials and methods

A descriptive and analytical observational cross-sectional study was performed on a population sample of non-elderly adults (between 20 and 59 years of age) voluntarily enrolled at the Clinical Medicine Service of the Hospital Privado Universitario de Cordoba (HPUC) between April 2014 and July 2015. A written informed consent was obtained from all individuals, and the study was approved by the local Ethics Committee of HPUC and conducted in accordance

with the Declaration of Helsinki. Individuals with CVD antecedents, diabetes mellitus, lipid-lowering drug treatment and pregnant women were excluded.

Data such as weight, height, waist circumference, smoking status (current, former or never smoked), family history of premature coronary artery disease (acute myocardial infarction or sudden death in first-degree relatives having occurred in males under the age of 55 years or females under 65 years), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were collected. In addition, blood samples were collected for laboratory tests that included: plasma glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and hemoglobin A1c. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m). Three categories of BMI were defined following NHLBI guidelines [15]: normal, 18.5–24.9 kg/$m^2$; overweight, 25–29.9 kg/$m^2$; and obese, ≥30 kg/$m^2$. At the time of medical consultation, all individuals provided pathological antecedents, such as: arterial hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or antihypertensive medication use), dyslipidemia (total cholesterol ≥200 mg/dl; HDL-c: <40 mg/dl in males and <50 mg/dl in females; or triglycerides ≥150 mg/dl).

## Framingham risk score 10-year risk (FRS 10) calculation and risk stratification

The FRS 10 H was calculated for hard coronary heart disease events (non-fatal myocardial infarction or coronary death) and the FRS 10 CVD was calculated for general CVD events (non-fatal myocardial infarction, coronary death, coronary insufficiency, angina pectoris, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease or heart failure) for individuals between 30 and 74 years of age following the Framingham study design. Individuals were stratified into different risk groups depending on the value of their FRS 10 as follows: low (<10%), intermediate (10–20%) and high (>20%) [4, 5].

## Framingham risk score 30-year risk (FRS 30) calculation and risk stratification

The FRS 30 was calculated based on lipid values (FRS 30 L) and the BMI values (FRS 30 BMI) for Hard CVD events (non-fatal myocardial infarction,

coronary death, or stroke) (FRS 30 L H and FRS 30 BMI H) and general CVD events (non-fatal myocardial infarction, coronary insufficiency, coronary death, angina pectoris, stroke, transient ischemic attack, heart failure, or peripheral artery disease) (FRS 30 L CVD and FRS 30 BMI CVD) following the Framingham study design [16]. Individuals were stratified into different risk groups depending on their FRS 30 values as follows: low (<12%), intermediate (12–40%) and high (>40%) [16].

## Calculation of Pooled Cohort ASCVD Risk Equations (PCE) and risk stratification

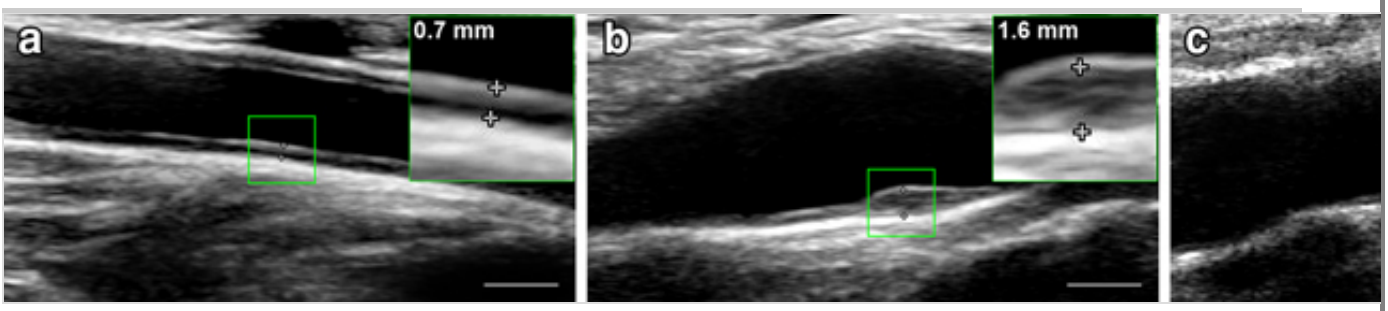
The 10-year PCE (PCE 10) was calculated for Hard ASCVD events (non-fatal myocardial infarction, coronary death or stroke) for individuals between 40 and 79 years of age following the American College of Cardiology/American Heart Association (ACA/AHA) guidelines [6]. Individuals were stratified into risk groups based on the PCE 10 values as follows: low (<5%), intermediate (5–7.4%) and high (>7.4%). In addition, the lifetime risk PCE (PCE LT) was also calculated [6].

## Carotid ultrasound (CU) study

The CU study was performed using Accuvix V10, Samsung Medison Co. Ltd. (Seoul, Korea) with a linear transduction of variable frequency from 5 to 13 MHz (Fig. 1). The distal segment of the common carotid artery, the carotid bulb and the proximal segment of the internal carotid artery were examined. The results from the CU were considered abnormal when an increased CIMT (>0.9 mm) or a carotid atherosclerotic plaque was detected [17]. The presence of a carotid atherosclerotic plaque was defined by: (a) CIMT >1.5 mm, (b) an abnormal structure (lumen protrusions and loss of alignment between adjacent walls), and (c) an abnormal wall echogenicity following the criteria of the Atherosclerosis Risk in Communities (ARIC) study [18]. The same imaging expert of the HPUC performed all CU procedures.

**Fig. 1**

Representative Carotid Ultrasound images depicting normal (**a**), increased CIMT (**b**), and carotid atherosclerosis plaque (**c**). All *lines* represent a scale of 4 mm. The overlaid images are magnified 2.5× (*boxed areas*)

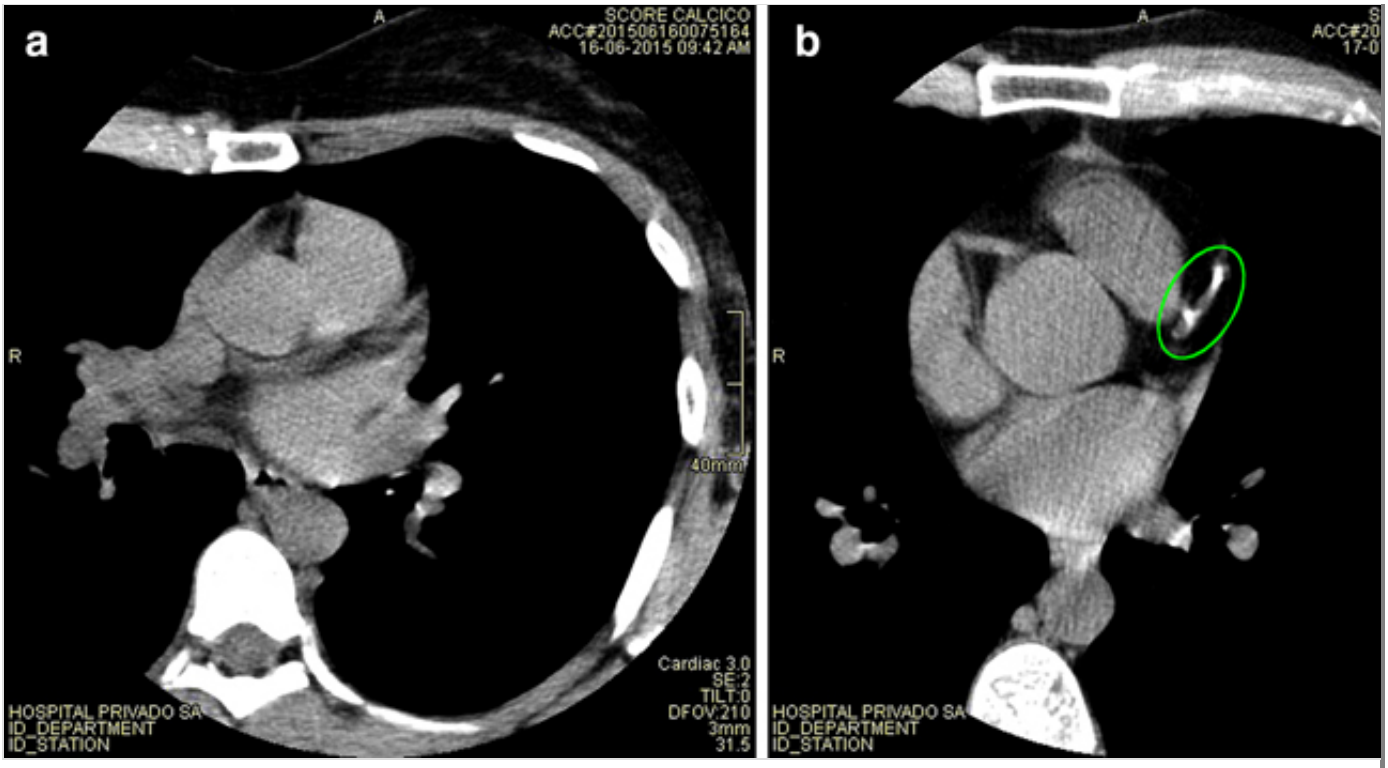



## Coronary artery calcium (CAC) score determination by cardiac computed tomography (CT)

Cardiac CT scans were performed using a Toshiba Aquilion helicoidal multidetector tomograph manufactured by Toshiba America Medical Systems, Inc. (Tustin, CA, USA), which has 16 detectors in line. The human chorionic gonadotropin (HCG) was assayed to detect pregnancy in females before performing Cardiac CT and only HCG-negative individuals were included in the study. All Cardiac CT procedures were performed by the same imaging expert of the HPUC using software validated to score the CAC. Based on the number of calcified lesions found in each subject, the CAC was determined using the Agatston method [19]. An abnormal CAC score was defined as >0 (Fig. 2).

**Fig. 2**

Representative images of cardiac computed tomography (CT) depicting normal (**a**) and calcified lesions in left coronary artery containing a calculated coronary artery calcium (CAC) score >0 (**b**)




## SA definition

Individuals with increased CIMT, a carotid atherosclerotic plaque or CAC >0.

## Statistical analysis

Data was expressed as mean ± standard deviation for continuous variables and as a percentage for categorical variables. The student *t* test was used to compare continuous parametrical data, with the Wilcoxon Mann–Whitney test being utilized for continuous non-parametrical data and the Chi square test used to analyze categorical data. For these tests, a $p$ value <0.05 was considered statistically significant. A receiver operating characteristic (ROC) analysis was performed to determine the area under the curve with Youden's index calculated to evaluate how the risk scores applied to our study population sample [20]. In addition, sensitivity (%), specificity (%), positive predictive value (PPV, %) and negative predictive value (NPV, %) were estimated and employed to modify the stratification of risk scores in order to adapt the predictive values to our study population.

# Results

In this study, 274 individuals were enrolled (143 male and 131 female), with the

clinical parameters and estimated CVD risk scores being shown in Table 1. When considering all the evaluated risk factors, we found that dyslipidemia was the most prevalent. For the clinical parameters, significant gender differences were observed in BMI, waist circumference, BP, HDL-c, LDL-c, and fasting plasma glucose. Moreover, the estimated CVD risk scores shown by male subjects were greater than those observed in females.

**Table 1**

Clinical parameters and estimated CVD risk scores of the population sample (n = 274)

| | **Total** | **Female** | **Male** | **P value** |
|---|---|---|---|---|
| Age (years) | 41.7 ± 10.8 | 43.0 ± 11.2 | 40.5 ± 10.4 | 0.0534 |
| BMI ($Kg/m^2$) | 25.9 ± 4.4 | 25.1 ± 5.0 | 26.6 ± 3.6 | 0.0039 |
| Waist circumference (cm) | 90.8 ± 11.2 | 87.2 ± 11.8 | 94.0 ± 9.5 | <0.0001 |
| SBP (mm Hg) | 117.7 ± 11.9 | 115.1 ± 12.5 | 120 ± 10.8 | 0.0006 |
| DBP (mm Hg) | 81.2 ± 8.1 | 78.5 ± 7.9 | 83.7 ± 7.4 | <0.0001 |
| Total cholesterol (mg/dl) | 193.2 ± 37.3 | 193.9 ± 37.8 | 192.6 ± 36.9 | 0.7837 |
| HDL cholesterol (mg/dl) | | 65.0 ± 18.5 | 46.6 ± 13.3 | <0.0001 |
| LDL cholesterol (mg/dl) | 119.7 ± 33.0 | 113.1 ± 31.8 | 125.7 ± 32.9 | 0.0014 |
| Triglycerides (mg/dl) | 116.8 ± 88.1 | 106.7 ± 106.3 | 125.9 ± 66.4 | 0.0711 |
| Fasting plasma glucose (mg/dl) | 97.5 ± 8.5 | 95.1 ± 8.5 | 99.6 ± 8.0 | <0.0001 |
| HbA1c (%) | 5.4 ± 0.4 | 5.4 ± 0.4 | 5.4 ± 0.4 | 0.9094 |
| FRS 10 H | 2.6 ± 3.6 | 1.2 ± 0.9 | 3.9 ± 4.6 | <0.0001 |
| FRS 10 CVD | 5.9 ± 5.5 | 3.8 ± 3.0 | 8.0 ± 6.6 | <0.0001 |
| PCE 10 | 3.2 ± 3.3 | 1.7 ± 1.6 | 5.0 ± 4.0 | <0.0001 |
| PCE LT | 35.7 ± 16.0 | 30.0 ± 13.4 | 40.9 ± 16.4 | <0.0001 |
| FRS 30 BMI H | 13.8 ± 12.0 | 10.1 ± 8.7 | 17.3 ± 13.5 | <0.0001 |
| | | | | |

| | | | | |
|---|---|---|---|---|
| FRS 30 L H | 12.6 ± 11.2 | 9 ± 8.3 | 15.8 ± 12.4 | <0.0001 |
| FRS 30 BMI CVD | 23.0 ± 16.5 | 18.6 ± 13.6 | 27.1 ± 17.9 | <0.0001 |
| FRS 30 L CVD | 21.5 ± 16.1 | 17.2 ± 14.0 | 25.3 ± 17.1 | <0.0001 |
| **Categorical variable** | | **n (%)** | **n (%)** | |
| Hypertension | 18.25% | 17 (12.98%) | 33 (23.08%) | 0.0412 |
| Dyslipidemia | 55.84% | 66 (50.4%) | 87 (60.8%) | 0.0892 |
| Current smoking | 19.71% | 22 (16.79%) | 32 (22.38%) | 0.2880 |
| Obesity | 14.60% | 16 (12.21%) | 24 (16.78%) | 0.3083 |
| Metabolic syndrome | 20.07% | 20 (15.27%) | 35 (24.48%) | 0.0699 |

*BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *HbA1C* hemoglobin A1c, *FRS* Framingham Risk Score, *FRS 10 H* 10-year Hard Coronary Heart Disease Framingham risk score, *FRS 10 CVD* 10-year general cardiovascular disease Framingham risk score, *PCE 10* 10-year pool cohort equations hard cardiovascular disease, *PCE 10 LT* lifetime (30-years) pool cohort equations for hard atherosclerotic cardiovascular disease, *FRS 30 BMI* or *L H* 30-year hard cardiovascular disease body mass index (BMI) or lipid (L) Framingham Risk score, *FRS 30 BMI* or *L CVD* 30-year cardiovascular disease body mass index (BMI) or lipid (L) Framingham Risk score

SA was detected in 32.4% of the individuals (38.4% male and 25.9% female). Abnormal CU was found in 24.5% of subjects, increased CIMT in 23% and carotid atherosclerotic plaque in 6.5% of individuals, but with no gender differences revealed. The CAC scores by Cardiac CT were found to be >0 in 15.8% of subjects (26% male and 4.6% female), with 2.5% of individuals (4.2% male and 0.7% female) showing a CAC score >100. Considering the total positive CAC, five of six females presented an abnormal CU, whereas for males this occurred in 16 of 37.

The clinical parameters and estimated CVD risk scores related to the absence or presence of SA are described in Table 2. Considering the risk factors, significant differences were observed for hypertension, dyslipidemia, and metabolic syndrome between these two groups. For the clinical parameters,

higher values for the group with SA (except for HDL-c) were observed, and in agreement, the estimated CVD risk scores were significantly higher for the group with SA.

**Table 2**

Clinical parameters and estimated CVD risk scores related to SA (n = 274)

| | **Absence of SA n = 185** | **Presence of SA n = 89** | **P value** |
|---|---|---|---|
| Age (years) | 38.0 ± 10.4 | 49.2 ± 7.5 | <0.0001 |
| BMI (kg/m$^2$) | 25.5 ± 4.6 | 26.7 ± 3.7 | 0.0296 |
| Waist circumference (cm) | 89.0 ± 11.8 | 94.5 ± 8.7 | <0.0001 |
| SBP (mmHg) | 116.6 ± 11.7 | 119.8 ± 12.0 | 0.0356 |
| DBP (mmHg) | 80.3 ± 8.2 | 83.0 ± 7.4 | 0.0079 |
| Total cholesterol (mg/dl) | 186.6 ± 36.3 | 206.9 ± 35.6 | <0.0001 |
| HDL cholesterol (mg/dl) | 58.3 ± 19.3 | 49.4 ± 14.8 | 0.0002 |
| LDL cholesterol (mg/dl) | 112.6 ± 32.0 | 134.2 ± 30.3 | <0.0001 |
| Triglycerides (mg/dl) | 108.1 ± 93.1 | 134.7 ± 74.2 | 0.0191 |
| Fasting glucose (mg/dl) | 95.7 ± 7.7 | 101.1 ± 9.1 | <0.0001 |
| HbA1C (%) | 5.4 ± 0.3 | 5.5 ± 0.4 | 0.0012 |
| FRS 10 H | 1.7 ± 2.2 | 4.5 ± 5.0 | <0.0001 |
| FRS 10 CVD | 4.1 ± 3.7 | 8.7 ± 6.6 | <0.0001 |
| PCE 10 | 2.1 ± 2.5 | 4.4 ± 3.8 | <0.0001 |
| PCE LT | 32.2 ± 16.2 | 42.8 ± 13.0 | 0.0009 |
| FRS 30 BMI H | 9.8 ± 8.8 | 22.2 ± 13.4 | <0.0001 |
| FRS 30 L H | 15.5 ± 12.7 | 33.8 ± 15.5 | <0.0001 |
| FRS 30 BMI CVD | 17.3 ± 13.1 | 34.9 ± 16.6 | <0.0001 |
| FRS 30 L CVD | 15.5 ± 12.7 | 33.8 ± 15.5 | <0.0001 |
| **Categorical variable** | **n (%)** | **n (%)** | |
| Hypertension | 23 (12%) | 27 (30%) | <0.0001 |

| | | | |
|---|---|---|---|
| Dyslipidemia | 91 (49%) | 62 (69%) | 0.0018 |
| Current smoking | 32 (17%) | 22 (24%) | 0.1940 |
| Obesity | 25 (13%) | 15 (17%) | 0.4695 |
| Metabolic syndrome | 24 (13%) | 31 (35%) | <0.0001 |

*BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *HbA1C* hemoglobin A1c, *FRS 10 H* 10-year Hard Coronary Heart Disease Framingham risk score, *FRS 10 CVD* 10-year general cardiovascular disease Framingham risk score, *PCE 10* 10-year pool cohort equations hard cardiovascular disease, *PCE 10 LT* lifetime (30-years) pool cohort equations for hard atherosclerotic cardiovascular disease, *FRS 30 BMI* or *L H* 30-year hard cardiovascular disease body mass index (BMI) or lipid (L) Framingham Risk score, *FRS 30 BMI* or *L CVD*30-year cardiovascular disease body mass index (BMI) or lipid (L) Framingham Risk score

All the CVD risk scores of this study were analyzed and compared with the presence of SA using ROC curves (Suppl Fig. 1). In Table 3, the area under the curve together with Youden's index is shown for each CVD risk score. From these data, the two CVD risk scores that showed the biggest areas under the ROC curve were FRS 30 L H and FRS 30 L CVD, which were higher than most commonly used CVD risk scores in clinical practice, such as FRS 10 H, PCE 10 and PCE LT. The presence of SA and the values of the CVD risk score stratification following the established cutoff values [4, 5, 6] are shown in Table 4. In the case of FRS 10 H, the majority of individuals were considered to have a low risk although a high percentage (30.1%) of them demonstrated the presence of SA with 4.6% (female) and 22.4% (male) being positive for CAC. For the PCE 10 risk score, 79.5% of individuals were considered low, but had a 40.6% SA. For the PCE LT risk score, only 18.2% of subjects were considered low risk with a low prevalence found (10%) of SA. In contrast, the FRS 30 L H, 59.1% of individuals were in the low risk category, with 12.3% showing SA. Finally, for FRS 30 L CVD, 33.6% of subjects were observed to be within the low risk category, and had a very low prevalence (1.1%) of SA.

**Table 3**

CVD risk scores versus ROC curves

| | ***ROC* curve analysis results** |
|---|---|

| Risk score | Area under the curve | Cutoff value *Youden*'s index |
|---|---|---|
| FRS 30 L H | 0.85 | >8 |
| FRS 30 L CVD | 0.84 | >15 |
| FRS 30 BMI H | 0.83 | >10 |
| FRS 30 BMI CVD | 0.83 | >18 |
| FRS 10 H | 0.81 | >0.9 |
| FRS 10 CVD | 0.79 | >3.3 |
| PCE 10 | 0.75 | >1.4 |
| PCE LT | 0.68 | >36 |

*ROC* receiver operating characteristic, *FRS 10 H* 10-year Hard Coronary Heart Disease Framingham risk score, *FRS 10 CVD* 10-year general cardiovascular disease Framingham risk score, *FRS 30 BMI* or *L H* 30-year hard cardiovascular disease body mass index (BMI) or lipid (L) Framingham Risk score, *FRS 30 BMI* or *L CVD* 30-year cardiovascular disease body mass index (BMI) or lipid (L) Framingham Risk score, *PCE 10* 10-year pool cohort equations hard cardiovascular disease, *PCE LT* lifetime (30-years) pool cohort equations for hard atherosclerotic cardiovascular disease

**Table 4**

Stratification by CVD risk scores versus SA

| Risk scores | Total | Absence of SA | Presence of SA |
|---|---|---|---|
| FRS 10 H | | | |
| Low [n (%)] | 262 (95.6) | 183 (69.8) | 79 (30.2) |
| Intermediate [n (%)] | 10 (3.6) | 2 (20%) | 8 (80%) |
| High [n (%)] | 2 (0.7) | 0 (0%) | 2 (100%) |
| PCE 10 | | | |
| Low [n (%)] | 128 (79.5) | 76 (59.4) | 52 (40.6) |
| Intermediate [n (%)] | 19 (12%) | 6 (31.6) | 13 (67.7) |
| High [n (%)] | 14 (8.7) | 3 (21.4) | 11 (78.5) |
| PCE LT | | | |

| | | | |
|---|---|---|---|
| Low [n (%)] | 50 (18.3) | 45 (90) | 5 (10) |
| Intermediate [n (%)] | 129(47.3) | 89 (69.0) | 40 (31) |
| High [n (%)] | 94 (34.4) | 51 (54.3) | 43 (45.7) |
| FRS 30 L H | | | |
| Low [n (%)] | 162 (59.1) | 142 (87.7) | 20 (12.3) |
| Intermediate [n (%)] | 102 (37.2) | 42 (41.2) | 60 (58.8) |
| High [n (%)] | 10 (3.7) | 1 (10.0) | 9 (90.0) |
| FRS 30 L CVD | | | |
| Low [n (%)] | 92 (33.6) | 91 (98.9) | 1 (1.1) |
| Intermediate [n (%)] | 148 (54.0) | 83 (56.1) | 65 (43.9) |
| High [n (%)] | 34 (12.4) | 11 (32.4) | 23 (67.7) |

*FRS 30 L CVD* 30-year cardiovascular disease lipid (L) Framingham Risk score, *FRS 10 H* 10-year Hard Coronary Heart Disease Framingham risk score, *PCE 10* 10-year pool cohort equations hard cardiovascular disease, *PCE LT* lifetime (30-years) pool cohort equations for hard atherosclerotic cardiovascular disease, *FRS 30 L H* 30-year hard cardiovascular disease lipid (L) Framingham Risk score

From the ROC analysis, the cut-off values were recalculated using PPV and NPV for our local population sample, with the presence of SA with adjusted CVD risk scores calculated using the new cutoff values shown in Table 5. Based on these data, low, intermediate and high risk score groups were re-defined. The new cutoff values for FRS 30 L H(a) were <9%, 9–40% and >40% for low, intermediate and high risk, respectively, whereas for FRS 30 L CVD(a) the values were <12%, 12–52% and >52%. Using the adjusted FRS 30 L H(a) 46% of subjects had a low risk score with 4% SA prevalence, and 3.7% of individuals were high risk with 90% SA prevalence. In addition, the adjusted FRS 30 CVD(a) included 33.6% of subjects in the low risk score group with a very low prevalence (1.1%) of SA, while 5.1% of individuals fell into the high risk category an 85.7% SA prevalence.

**Table 5**

Stratification by adjusted CVD risk scores versus SA

| Adjusted CVD risk scores (a) | Total | Absence of SA | Presence of SA |
|---|---|---|---|
| FRS 30 L H (a) | | | |
| Low [n (%)] | 126 (46) | 121 (96.0) | 5 (4.0) |
| Intermediate [n (%)] | 138 (50.3) | 63 (45.7) | 75 (54.3) |
| High [n (%)] | 10 (3.7) | 1 (10) | 9 (90.0) |
| FRS 30 L CVD (a) | | | |
| Low [n (%)] | 92 (33.6) | 91 (98.9) | 1 (1.1) |
| Intermediate [n (%)] | 168 (61.3) | 92 (54.8) | 76 (45.2) |
| High [n (%)] | 14 (5.1) | 2 (14.3) | 12 (85.7) |

*FRS 30 L CVD (a)* adjusted 30-year cardiovascular disease lipid (L) Framingham Risk score; *FRS 30 L H (a)* adjusted 30-year hard cardiovascular disease lipid (L) Framingham Risk score

# Discussion

Cardiovascular disease risk scores are very important tools in clinical practice because they help with the decision making process in therapy as well as with optimization of the use of available resources [21]. One of the most commonly used risk scores has been the FRS 10 H. However, it has some limitations, with one of these being the need to adjust its value to each local population [8]. This limitation led to the ~~the~~ ACC/AHA proposing PCE 10, with values that were applicable to the African American population but not valid for the Hispanic population [6]. In fact, both FRS 10 H and the PCE 10 overestimate the cardiovascular disease risk for the Hispanic population [22, 23]. Moreover, there are few studies that can help to adjust these values [8], highlighting the need for more investigations to be performed in Latin America. Another limitation that arises from these studies is that FRS 10 H underestimates the coronary risk for female and young adults, which gave rise to the risk scores for 30-years or lifetime [16]. For these reasons, the use of FRS 10 H and the PCE 10 were not appropriate for evaluating our population. For example, the low risk group defined by these variables showed a moderate prevalence of SA (30 and 40% respectively). Previous studies have also detected a moderate to high prevalence of SA in low risk groups defined by FRS 10 H (32–77%), albeit with the elderly individuals being caucasian, Mexican or Brazilian populations,

which can differ demographically from our sample population [24, 25, 26]. In addition, the values for FRS 10 H and SA prevalence estimated by CU in our study were in line with those observed in an investigation performed in a different region of our country with similar population demographics [27]. With respect to SA prevalence by CAC our results for individuals with a low risk of FSR 10H also revealed a similar percentage of CAC as those obtained by the CARDIA and MESA studies on individuals with low FSR 10H and an age <50 year [28]. In the CARDIA study positive CAC values of 13.3% in males and 4.6% in females were obtained, whereas in the MESA study, these figures were 26.2 and 19.0%, respectively. Since our sample population consisted of non-elderly adults, we found the CVD risk scores that best reflected the detected prevalence of SA were the FRS 30-year ones, placing our sample population in the low risk group with a very low prevalence of SA [24, 25, 27].

Detecting SA improves the predictive power of the CVD risk scores, particularly for patients that are in the intermediate risk groups [29]. However, the presence and the severity of SA has shown a strong dependence on the demographic composition of the population, namely race and ethnicity [30], and since these CVD risk scores predict the chance of suffering cardiovascular disease, but not the prevalence of SA, it is very important to have the CVD risk scores adjusted and validated for our population in order to appropriately define each CVD risk group. Using the ROC curve analysis we observed that FRS 30 L H and FRS 30 L CVD were the risk scores that were better associated with the presence of SA in the non-elderly adult population. Then, by applying Youden`s index to these ROC curves, we adjusted FRS 30 L H and L CVD to improve the NPV and PPV for non-elderly adults. In the case of FRS 30 L H, the low risk group showed a good negative predictive value (NPV = 87.7%) that was further improved (NPV = 96%) when the corresponding cutoff for that group (<12%) was lowered (<9%). However, there was no need to adjust the cutoff value for the high risk group (<40%), which already had a good PPV (90%). By adjusting the cutoff value of the low risk group, it is possible to avoid the need to use imaging to detect SA in 49.7% of the study population. In the case of the FRS 30 L CVD, the risk score had a good NPV for the low risk group (98.9%) and a PPV for the high risk group (69.7%) which was improved when the cutoff value (<40%) was increased (<52%) resulting in an optimal PPV (85.7%). Also, by adjusting the cutoff value of the high risk group, it is possible to avoid the

necessity of using imaging to detect SA in roughly 39% of subjects.

Interestingly, we observed gender differences for the prevalence of SA in our imaging studies. In the case of female individuals with SA all but one presented abnormal CU. In contrast, we found only 2/3 male individuals in which SA could be detected using only one method. Therefore, our results suggest that SA should only be studied by CU in non-elderly females, without performing Cardiac CT, whereas both studies should be performed in non-elderly males. Nonetheless, further studies including a larger number of subjects are necessary to confirm these conclusions.

# Limitations

We believe that our study has as a limitation in that our CVD risk scores were adjusted based on the prevalence of SA and not on the prevalence of cardiovascular events. A longitudinal study would definitively demonstrate whether our clinical and laboratory data for evaluating the presence of SA correlate with the occurrence of cardiovascular events. Finally, another limitation is that our sample of individuals is not representative of all regions of our country.

# Conclusions

The CVD risk stratification of non-elderly adults using FRS 30 L H and CVD may be a useful tool to select candidate patients for diagnostic imaging studies to assess their SA prevalence.

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Compliance with ethical standards

*Conflict of interest* R.A.A., D.G.F., P.A.R., M.E.T., J.L.A., R.C. and G.A.C. declare that they have no conflict of interest.

## Electronic supplementary material

Below is the link to the electronic supplementary material.

Supplementary material 1 (PDF 146 KB)

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