# Applicability of the Framingham 30-year risk score based on body mass index. Usefulness in cardiovascular risk stratification and diagnosis of carotid atherosclerotic plaque

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## SUMMARY

### Background
The traditional Framingham 10-year risk score (FS10) underestimates cardiovascular risk in certain populations. Extending its time-scale to 30 years and assessing its relationship with the presence of carotid atherosclerotic plaque (CAP) may improve risk stratification.

### Objective
1) To determine the percentage of patients previously classified with the FS10 who were reclassified when using Framingham 30-year risk score based on body mass index (FS30I); 2) to evaluate the consistency between both methods of classification; 3) to analyze the prevalence of CAP stratified by the FS30I; and 4) to determine the diagnostic potential of the FS30I to detect CAP.

### Material and Methods
A carotid Doppler ultrasound study was performed and the FS10 and FS30I for "hard" cardiovascular events were calculated in a population of primary prevention patients. The prevalence of CAP was determined. Receiver operating characteristic analysis and the consistency between both methods of classification were evaluated.

### Results
A total of 410 subjects were included (age 48±11 years, 54% were men, 79% had low risk according to the FS10). The FS30I reclassified 64% of the total population and 66% of the low-risk subgroup. The prevalence of CAP was 28% and was gradually associated with the risk category. The area under the curve and optimal cutoff points of the FS30I to detect CAP were 0.862 and 21%, respectively. The consistency between FS10 and FS30I was low (kappa 0.15).

### Conclusions
The 30-year score reclassified a large number of patients and discriminated between those with or without evidence of carotid plaques.

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Abbreviations >

| | | | |
|---|---|---|---|
| **HDL-C** | High density lipoprotein cholesterol | **FS30** | Framingham 30-year risk score |
| **SD** | Standard deviation | **FS30I** | Framingham 30-year risk score based on body mass index |
| **IMT** | Intima-media thickness | | |
| **BMI** | Body mass index | **FSdelta** | Difference between the scores observed and expected according to age and gender. |
| **CAP** | Carotid atherosclerosis plaque | | |
| **OCP** | Optimal cut-off point | **ROC** | Receiver operating characteristic |
| **FS10** | Framingham 10-year risk score | **NPV** | Negative predictive value |
| **FS10I** | Framingham 10-year risk score based on body mass index | **PPV** | Positive predictive value |

## BACKGROUND

Cardiovascular disease is the main cause of morbidity and mortality. (1) Evaluation of cardiovascular risk is the most appropriate way to discriminate between individuals who require intensive measures to control their risk factors and those who do not need them because they are at very low risk. Large-scale prospective epidemiological studies have given rise to multivarite models, from which clinical prediction equations were designed. (2-7) Functions or scores for calculating cardiovascular risk are extremely useful tools in clinical practice, but they have limitations in their capacity to calibrate and discriminate the model. (8, 9) The cohort study based on the American city of Framingham began in 1948 and determined the design of the most commonly used risk function, the Framingham 10-year risk score (FS10). (2, 10) The third report of the National Cholesterol Education Program (NCEP) Panel of Experts on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) incorporated FS10 as key tool in cardiovascular risk stratification. (11) However, such score presents certain weaknesses, basically the fact that it underestimates cardiovascular risk in certain populations, such as the young or women. Considering that most cardiovascular events occur in populations at low or moderate risk, (12) it is necessary to have access to more efficient predictive tools. An option is to extend the period to predict vascular events, thus givinig physicians and patients a different perspective of the problem. It has recently been published a new function (based on descendants of the original Framingham cohort) that extends the time-scale from 10 to 30 years (SF30). (13) Two models were designed: one based on blood lipid concentrations (total cholesterol and HDL-C), and the other based on body mass index (BMI). The latter has the advantage that it does not requiere lab tests and can be performed simply with data obtained from a patient medical history and clinical examination. Another alternative is the inclusion of new prognostic elements (biomarkers or diagnostic methods that identify subclinical atherosclerosis) into cardiovascular risk estimations based on typical risk factors. The diagnosis of carotid atherosclerotic plaque (CAP) through Doppler is a surrogate objective and constitutes an independent predictor of coronary events. Unfortunately, due to limited availability of resources or increased costs, CAP detection methods cannot be applied in all healthcare centers. Taking into account the aforementioned, the objectives of our study were the following: 1) To determine how many patients analyzed with FS10 were reclassified on applying FS30 based on BMI (FS30I); 2) to evaluate the consistency between both methods of classification; 3) to analyze the prevalence of CAP in a population stratified by FS30I; and 4) to determine the optimal cut-off point (OCP) of FS30I to discriminate betweeen individuals with or without evidence of CAP.

## MATERIAL AND METHODS

### Design

A descriptive-analytical, cross-sectional, observational study was conducted. The sample was obtained with a non-probabilistic model in the Cardiovascular Prevention clinic of the Caridology Department of Hospital Italiano, Buenos Aires.

### Inclusion and exclusion criteria

Subjects under 60 years of age were included (age limit that enables to calculate FS30 risk). Exclusion criteria were the following: 1) previous cardiovascular disease (acute myocardial infarction, unstable angina, chronic stable angina, myocardial revascularization surgery, coronary angioplasty, stroke, peripheral vascular disease, or aortic disease), 2) personal history of diebetes mellitus, and 3) previous lipid-lowering therapy.

### Definition of variables

The FS10 was calculated (defining low, moderate or high risk as < 10%, 10% -19%, and ≥ 20% risk, respectively), and FS30I was calculated for "hard" events: acute myocardial infarction, death due to coronary cause, and stroke. By applying FS30I, the difference between the expected or "normal" risk for age and gender (absent risk factors with optimal plasma and blood pressure values) and the observed or "real" score obtained in each subject in particular (FSdelta) was determined. The number of patients reclassified by the new score was calculated, which was based on low risk defined as ≤ 12%, and high risk defined as ≥ 40%. Such scores are drawn from the original publication by Pencina et al in 2009. (13) CAP was defined as an atherosclerotic plaque in the carotid arteries, from images obtained during noninvasive bi-dimensional mode ultrasound images, using a LOGIQ Book XP Ultrasound System (General Electric™), with a 7.5 MHz linear transducer. Presence of plaque was defined when the following requisites were met: 1) abnormal wall thickness (defined as an intima-media thickness (IMT) > 1.5 mm), 2) abnormal structure (protrusion towards the lumen, loss of alignment with the adjacent wall), and 3) abnormal wall echogenicity. Prevalence of CAP in the different risk categories was compared.

### Statistical analysis

A ROC (receivier operating characteristic) analysis was performed to determine the area under the curve and evaluate how accurately FS30I and FSdelta scores discriminate between subjects with or without CAP. To determine the OCP of SF30I and FSdelta to detect CAP, Younden's index was used, which corresponds to the maximum vertical distance between the ROC cuve and the statistical chance line (CJ point). (14) Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Continuous data for two groups were analyzed with the t test when the distribution of variables was normal, or with the Wilcoxon Mann-Whitney test when it was not. Categorical data were analyzed with the chi-square test. Concordance between the two classification methods and the impact in terms of change of percentage distribution between "low" or "non-low" risk categories were analyzed with Cohen's kappa index. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as percentages. A value of P < 0.05 was considered statistically significant.

**Ethical considerations**

The study was conducted following the Declaration of Helsinki – Ethical Principles for Medical Research, the Good Clinical Practice Guidelines, and our local Ethics Committee regulations. The analysis of data was totally anonymous.

**RESULTS**

A total of 410 patients were enrolled (222 men and 188 women), aged 48 ± 11 years. According to the FS10 score, 79% of the study population had low risk, and only 2% were categorized as high risk. Table 1 shows the characteristics of the study population.

The (mean ± SD) FS30I score was 22.1% ± 14% (men: 26.6% ± 14%; women: 17% ± 9%), while for PFdelta corresponded 8.1% ± 9% (men: 10.6% ± 9.6%; women: 5,6% ± 7,6%).

**Stratification and recategorization of cardiovascular risk**

The FS30I score classified 28%, 58%, and 14% of the patients as being at low, moderate, and high risk, respectively. This function reclassified 64% of the population analyzed with respect to their FS10 scores (Figure 1). Among the low-risk subgroup, 66% of the subjects changed their category (64% as moderate risk, and 2% as high risk). A 65% of low-risk women were recategorized as moderate risk, and only one patient was reclassified as high risk. On the other hand, among low-risk men, 63% and 4% were recategorized as moderate and high risk, respectively.

Concordance in "low" or "not low" risk classification was very poor when comparing FS10 with PF30I (kappa 0.15).

**Prevalence of CAP by risk categories**

Overall prevalence of CAP was 28%. When analyzing the population with FS10, the prevalence of CAP was 19%, 60%, and 100% in subjects with low, moderate, and high risk, respectively (p < 0.0001). With FS30I, the prevalence of CAP was: 3% with low risk (men 2%, women 3%), 29% moderate risk (men 24%, women 33%), and 75% high risk (men 76%, women 100%) (p < 0.0001).

A positive correlation between the FS30I deciles and the CAP prevalence was found (Figure 2).The (mean ± SD) FS30I score was significantly higher (34.4% ± 14% versus 17.3% ± 11%; p < 0.001) in subjects with CAP, compared with individuals without CAP. In the same way, FSdelta was higher in subjects with CAP (15.4% ± 10% versus 5.3% ± 7%; p < 0.001) (Figure 3).

**ROC Analysis**

The area under the curve for FS30I to detect CAP was 0.832 (CI 95% 0.791-0.874, Younden's index 0.52), and the OCP was ≥ 21% (sensitivity 83%, specificity 69%, PPV 51%, NPV 91%) (Figure 4). A high cut-off point for high sensitivity was explored (13%, sensitivity 97%), and another one for high specificity (44%, specificity 98%). The NPV of the first one was 97%, and the PPV of the second one was 83%.

On the other hand, the area under the FSdelta curve

| | Men (n = 222) | Women (n = 188) | Total (n = 410) |
|---|---|---|---|
| **Continuous variables, mean (SD)** | | | |
| Age, years | 45 ± 12 | 50 ± 9 | 48 ± 11 |
| Systolic blood pressure, mm Hg | 127 ± 14 | 126 ± 12 | 127 ± 13 |
| Total cholesterol, mg/dl | 221 ± 47 | 224 ± 38 | 222 ± 43 |
| HDL-C, mg/dl | 147 ± 40 | 147 ± 40 | 147 ± 40 |
| HDL-C, mg/dl | 42 ± 11 | 56 ± 14 | 48 ± 14 |
| Triglycerides, mg/dl | 159 ± 105 | 117 ± 58 | 140 ± 90 |
| Apolipoprotein B, mg/dl | 113 ± 33 | 108 ± 30 | 110 ± 31 |
| Apolipoprotein A1, mg/dl | 128 ± 24 | 160 ± 29 | 146 ± 31 |
| C-reactive protein, mg/dl | 1.47 ± 1.3 | 1.77 ± 1.9 | 1.66 ± 1.7 |
| Body mass index | 27.6 ± 3 | 25.3 ± 4 | 26.7 ± 4 |
| Glucose level, mg/dl | 98 ± 11 | 94 ± 10 | 96 ± 12 |
| **Categorical variables, n (%)** | | | |
| Smokers | 48 (22) | 35 (17) | 83 (20) |
| Antihypertensive treatment | 77 (35) | 52 (28) | 129 (32) |
| FS10 | | | |
|   Low risk | 147 (66) | 179 (95) | 325 (79) |
|   Moderate risk | 67 (30) | 9 (5) | 77 (19) |
|   High risk | 8 (4) | 0 (0) | 8 (2) |
| FS30I | | | |
|   Low risk | 50 (23) | 63 (34) | 113 (28) |
|   Moderate risk | 116 (52) | 123 (65) | 239 (58) |
|   High risk | 56 (25) | 2 (1) | 58 (14) |

**Table 1.** Characteristics of the study population

SD: Standard deviation. HDL-C: Low density lipoprotein cholesterol HDL-C: High density lipoprotein cholesterol. FS10: Framingham 10-year score. FS30I: Framingham 30-year score based on body mass index.

to detect CAP was 0.799 (CI 95% 0.744-0.847, Younden's index 0.51), and the OCP was ≥ 8% (sensitivity 80%, specificity 72%, PPV 53%, NPV 90%).

## DISCUSSION

Most of the risk score equations used around the world estimate the risk for developing a cardiovascular event within 10 years. On this time-scale, approximately 80% of the cardiovascular events occur in individuals with low baseline risk. (12) The FS10 is unable to identify subjects with high vascular risk among men aged < 40 years, and classifies most women < 70 years as being of low cardiovascular risk. (15, 16) In recent years, two strategies to solve such problem have been developed: The first is to find biomarkers that improve the predictive power of a model based on traditional risk factors. (7) The second strategy is the detection of subclinical carotid atherosclerosis, or atherosclerosis in another vascular territory through imaging studies (for instance, calculating the coronary

calcium score by computed tomography, or measuring the ankle-brachial index or the IMT/carotid plaque by ultrasound). (17-19) A meta-analysis showed that the relative risk of acute myocardial infarction increases by 10% every 0.1 mm increase in IMT, independently of the typical risk factors. (20) In addition, there is a correlation between the IMT and the cardiovascular risk estimated by the FS10. (21, 22) A study carried out in our country, Argentina, reported that 1 in 2 patients initially considered as being at low cardiovascular risk with different clinical prediction tables was reclassified after CAP had been detected by echo-Doppler. (23) The prevalence of carotid plaques observed in our study is lower than that in the aforementioned study (28% versus 53%), but is consistent with other international publications, (24) probably because of the differences either in populations or in criteria used to define "plaque". In our study, CAP detection was gradually associated with risk category, regardless of the score used; however, the prevalence of CAP in the low-risk category was significantly higher when using the function at 10 years (approximately 1 in 5 patients). A recent review including 13,145 subjects showed that the inclusion of IMT and the presence or absence of CAP into a model consisting of traditional risk factors improved the cardiovascular event predictions. (25) The presence of CAP predicted the risk of ischemic heart disease better than IMT; this reaffirms the concept that when detecting a plaque we are not evaluating only a surrogate objective but also a process that in itself confirms the onset of atherosclerotic disease. In this study, 37.5% of the patients with 5%-10% risk (based on typical risk factors) and 38% of the
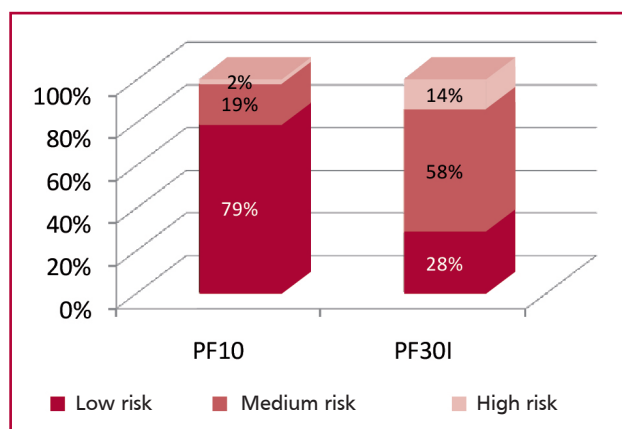


**Fig. 1**. Risk categories according to FS10 and FS30I scores. FS10: Framingham 10-year score. FS30I: Framingham 30-year score based on body mass index.
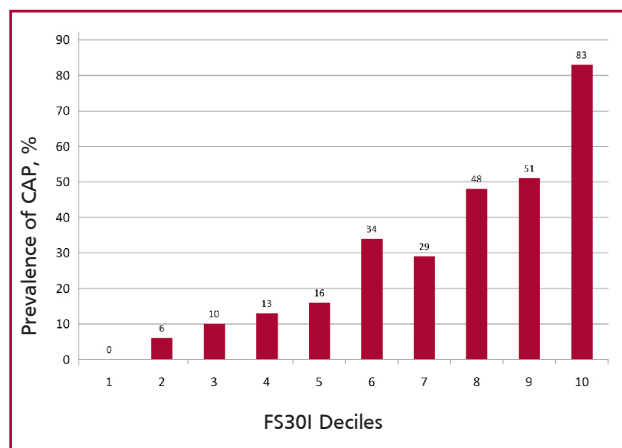


**Fig. 2**. Relation between the deciles for FS30I and the prevalence of CAP. CAP: Carotid atherosclerosis plaque. FS30I: Framingham 30-year score based on body mass index.
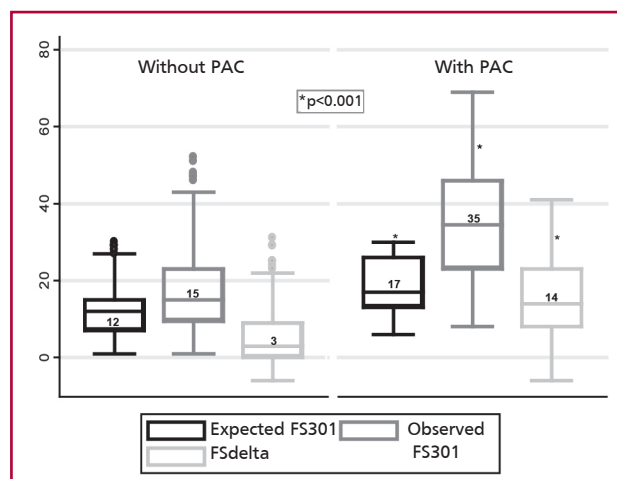


**Fig. 3**. Diagram of the box that shows the distribution of FS30I (observed and expected) and the FSdelta among subjects with and without CAP. Box limits represent the percentiles 25 and 75, and the line that crosses it represents the median. P value among individuals with or without CAP. CAP: Carotid atherosclerosis plaque. FS30I: Framingham 30-year score based on body mass index. FSdelta: Difference between the Framingham score at 30 years based on the body mass index observed and the expected according to gender and age.
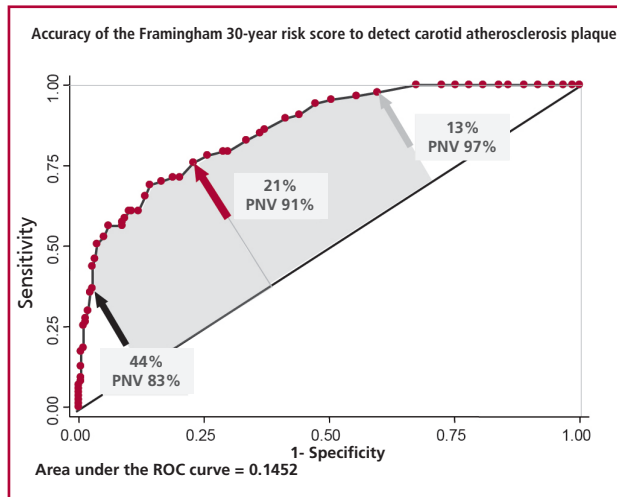
**Fig. 4.** Accuracy of the FS30i to detect CAP. The red arrow indicates the location of the OCP, the black arrow indicates the exploratory cut-off for high specificity, and the grey arrow, that for high sensitivity. See explanation in the text. CAP: Carotid atherosclerosis plaque. OCP: Optimal cut-off point. FS30I: Framingham 30-year score based on body mass index. NPV: Negative predictive value. PPV: Positive predictive value.

subjects with 10% -20% risk were reclassified when the information provided by carotid echo-Doppler was taken into account. Finally, some recently published guidelines formally classify patients with subclinical carotid atherosclerosis as high risk, and recommend preventive measures as intensive as those for any other patient under secondary prevention. (26)

However, bearing in mind the healthcare reality in many countries, chances of carotid echo-Doppler being widely used to detect incipient atherosclerosis and, therefore, "adjust" our patients' risk categories is debatable, to say the least. (27) The possible access to equations that predict events on a longer time-scale, but based on traditional risk factors, such as the BMI –inexpensive and easily obtained–, constitutes an attractive option. It is well known that overweight and obesity increase mortality due to cardiovascular disease and all-cause mortality. (28, 29) In an European study, BMI independently predicted fatal and non-fatal cardiovascular events at 10 years. (30) Also, there is a gradual and independent association between BMI and subclinical carotid atherosclerosis in middle-aged women and in individuals > 50 years of age with BMI > 23 (31, 32).

Evaluation of long-term risk is particularly relevant in younger people, because if we only paid attention to the short-term risk, we would be discouraging their changes in lifestyle and their possible treatment in many of the cases. In our study, the FS30L reclassified 64% of the total population and 66% of the low-risk subgroup. Concordance between functions at 30 years and at 10 years in classifying or not the low-risk population was poor. The motivation

for implementing preventive measures (and for their intensity) on the part of the physician, and for maintaining the adherence to treatment on the part of the patient is probably different according to the way in which baseline cardiovascular risk is presented.

In our study, the area under the ROC curve for FS30I to discriminate between individuals with or without CAP was good. The OCP $\geq$ 21% had high sensitivity. The NPV was high, indicating that if the FS30I is below the OCP, the likelihood of presenting CAP is low. An exploratory cut-off point of 13% increases sensitivity, which implies greater certainty to discard CAP. On the other hand, a cut-off point of 44% increases specificity, and therefore, the PPV for plaque detection. Observing the ROC curve, three areas with different clinical implications would remain. The extremes, below the exploratory cut-off point for high specificity and above the cut-off point for high sensitivity, accurately confirm or discard the presence of CAP. The area between the OCP and the exploratory cut-off point for high specificity corresponds to the points of greatest uncertainty in which CAP detection could add prognostic information. In this group, calculation of FSdelta would allow a second level of discrimination, because if such score was < 8%, the likelihood of not having CAP would be 90%. Finally, the area between the point of high sensitivity and the OCP corresponds to cut-off points that discriminate appropriately between subjects with or without carotid plaques, and requesting another method for confirming the presence of CAP will depend on the criteria of physicians, based on their clinical judgement and the conditions of the healthcare reality of the center in which they work.

**Limitations**

In our study, CAP diagnosis was performed using the ARIC (Atherosclerosis Risk in Communities) group criteria. However, there is no clear and uniform definition in the literature. (33) Changing the diagnostic criteria of plaque could modify our results.

Our study was not intended to validate whether risk reclassification is correct. A 30-year follow-up cohort study would be necessary for that purpose.

We believe a selection bias might exist in our sampling, as patients attending the cardiovascular prevention clinic do not represent the overall population.

The small proportion of high-risk patients would not be enough to draw conclusions about this subgroup of patients.

**Clinical implications**

Determining BMI is inexpensive and is easy to obtain; therefore, the FS30I score could be used in most medical centers of our country to improve primary prevention strategies, and thus reduce the need for investigating subclinical carotid atherosclerosis and the healthcare costs.

## CONCLUSION

In this primary prevention popoulation, the new FS30I reclassified a large number of patients. In addition, a strong association between the FS30I estimated risk and the prevalence of CAP was observed. The FS30I was useful in predicting the diagnosis of CAP, and perhaps in improving cardiovascular risk stratification in a low-risk population according to the traditional Framingham score, although this last hypothesis should be proved with studies to validate the risk functions.

## RESUMEN

**Función de Framingham a 30 años basada en el índice de masa corporal. Utilidad en la estratificación del riesgo cardiovascular y en el diagnóstico de placa aterosclerótica carotídea**

### Introducción
La función o puntaje de Framingham tradicional a 10 años (PF10) subestima el riesgo cardiovascular en ciertas poblaciones. Extender el horizonte temporal a 30 años y evaluar la relación con la presencia de placas ateroscleróticas carotídeas (PAC) podría mejorar la estratificación del riesgo.

### Objetivos
1) Determinar qué porcentaje de pacientes analizados con el PF10 se reclasifican con la aplicación del puntaje de Framingham a 30 años basado en el índice de masa corporal (PF30I). 2) Evaluar la concordancia entre los dos métodos de clasificación. 3) Analizar la prevalencia de PAC en una población estratificada por el PF30I. 4) Determinar la capacidad diagnóstica del PF30I para detectar PAC.

### Material y métodos
Se realizó un eco-Doppler carotídeo y se calcularon el PF10 y el PF30I para eventos cardiovasculares "duros" en una población de pacientes en prevención primaria. Se determinó la prevalencia de PAC. Se realizó un análisis ROC y se evaluó la concordancia entre los dos métodos de clasificación.

### Resultados
Se incluyeron 410 sujetos (edad 48 ± 11 años, 54% hombres, 79% de riesgo bajo según el PF10). El PF30I reclasificó al 64% de la población total y al 66% del subgrupo de riesgo bajo. La prevalencia de PAC fue del 28% y se asoció en forma gradual con la categoría de riesgo. El área bajo la curva y el punto de corte óptimo del PF30I para detectar PAC fueron 0,832 y 21%, respectivamente. La concordancia entre el PF10 y el PF30I fue baja (kappa 0,15).

### Conclusión
El puntaje a 30 años reclasificó a un gran número de pacientes y discriminó entre sujetos con o sin evidencia de placas carotídeas.

**Palabras clave >** Medición de riesgo - Obesidad - Arterias carótidas - Placa aterosclerótica

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