

# Use of Different Scores for Cardiovascular Risk Stratification in Primary Prevention and Their Implications in Statin Indication

## *Estratificación del riesgo cardiovascular con diferentes puntajes de riesgo en prevención primaria y sus implicaciones en la indicación de estatinas*

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### ABSTRACT

**Background:** Our setting lacks a cardiovascular risk score arising from a local epidemiological study, and so scores developed from great epidemiological studies in other regions are used. However, although these scores are very useful in clinical practice, they have limitations associated to calibration and discrimination capacity.

**Objectives:** The purpose of this study was to 1) to stratify cardiovascular risk in a primary prevention population using different scores; 2) to estimate the concordance between these scores; 3) to analyze statin use recommendations; and 4) to estimate the prevalence of atherosclerotic carotid plaque (CAP) and the optimal cut-off point (OCP) of the new American score (NS) to discriminate between subjects with or without CAP.

**Methods:** Primary prevention patients without diabetes or lipid-lowering therapy were included in the study. The Framingham score (FS), the European score (ES), the score recommended by the World Health Organization (WHOS) and the NS proposed by the new American guidelines were calculated, analyzing the concordance among them. The indication of statins was based on each score. Ultrasound was used to assess CAP occurrence. A ROC analysis was performed to analyze results.

**Results:** The study included 772 patients. Mean age was  $52 \pm 11$  years and 66% were women. According to FS, ES and WHOS, 78.8, 50.9% and 91.7% of the population were respectively classified at "low risk". A poor level of agreement between scores was found ( $\kappa$  0.14). The percentage of cases with absolute indication for statins based on FS, ES and NS was 23.6%, 7% and 33%, respectively. When there was no such indication and using the same scores, 23.5%, 50% and 18% of subjects had an optional recommendation. Applying WHOS, only 3% of patients would have been treated. The prevalence of CAP was greater in higher risk strata, though not negligible in low risk subjects. The OCP for the NS was 5.2%.

**Conclusion:** Risk stratification and the use of statins vary according to the cardiovascular score used. Knowledge of the relationship between presence of CAP and scores could improve the estimation of risk in our population.

**Key words:** Risk scores – Statins – Carotid atherosclerotic plaque.

### RESUMEN

**Introducción:** En nuestro medio no contamos con un puntaje de riesgo cardiovascular surgido de un estudio epidemiológico local, por lo que habitualmente se emplean puntajes desarrollados a partir de grandes estudios epidemiológicos de otras regiones que, si bien resultan herramientas muy útiles en la práctica clínica, tienen limitaciones relacionadas con la calibración y la capacidad de discriminación.

**Objetivos:** 1) Estratificar el riesgo cardiovascular de una población en prevención primaria utilizando diferentes puntajes. 2) Estimar la concordancia entre dichos puntajes. 3) Analizar la recomendación de estatinas. 4) Estimar la prevalencia de placa aterosclerótica carotídea (PAC) y el punto de corte óptimo (PCO) del nuevo puntaje americano (NP) que discrimine entre sujetos con PAC o sin PAC.

**Material y métodos:** Se incluyeron pacientes en prevención primaria, sin diabetes ni tratamiento hipolipemiente. Se calcularon los puntajes de Framingham (PF), europeo (PE), el recomendado por la OMS (POMS) y el propuesto por las nuevas guías americanas y se analizó la concordancia entre los diferentes puntajes. La indicación de estatinas se consideró en base a cada función de riesgo. La prevalencia de PAC se determinó mediante ultrasonido. Se realizó un análisis ROC.

**Resultados:** Se analizaron 772 pacientes (edad  $52 \pm 11$  años, 66% mujeres), de los cuales de acuerdo con los puntajes PF, PE y POMS se clasificaron de "riesgo bajo" el 76,8%, el 50,9% y el 91,7%, respectivamente. La concordancia fue pobre entre los tres puntajes ( $\kappa$  0,14). El 23,6%, el 7% y el 33% de los casos tenían indicación absoluta de estatinas en base al PF, el PE y el NP, respectivamente. Cuando no existía dicha indicación y utilizando los mismos puntajes, el 23,5%, el 50% y el 18% de los sujetos tenían una recomendación opcional. Aplicando el POMS, solo se trataría al 3% de los pacientes. La prevalencia de PAC fue más alta en los estratos de mayor riesgo, aunque no despreciable en sujetos con riesgo bajo. El PCO del NP fue 5,2%.

**Conclusiones:** La estratificación del riesgo y la indicación de estatinas varían según la función de riesgo utilizada. Conocer la relación entre la presencia de PAC y los puntajes podría mejorar la estimación del riesgo en nuestra población.

**Palabras clave:** Puntajes de riesgo - Estatinas - Placa aterosclerótica carotídea.

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## Abbreviations

ATP III	Adult Treatment Panel III	OCP	Optimal cut-off point
HDL-C	Cholesterol carried by high-density lipoproteins	ES	European score
LDL-C	Cholesterol carried by low-density lipoproteins	FS	Framingham score
NS	New American score	WHOS	Score recommended by the World Health Organization
WHO	World Health Organization	ROC	Receiver operating characteristic
CAP	Carotid atherosclerotic plaque		

## INTRODUCTION

A number of cardiovascular risk functions or scores have been developed from large epidemiological studies. (1-4) Although these scores are very useful clinical tools, they have limitations associated to calibration and discrimination capacity. (5) Unfortunately, there is no risk score arising from a local epidemiological study. The Cardiovascular Prevention Consensus published by the Argentine Society of Cardiology recommends using any risk score, (6) including the Framingham score (FS), the European score (ES) or the score recommended by the World Health Organization (WHOS) for countries in the region. (7)

New American guidelines (American College of Cardiology/American Heart Association) for cholesterol management were introduced at the end of 2013. (8) They recommend a new risk score (NS) based on old patient cohorts, indicating statin therapy to every patient between 40 and 75 years of age with risk  $\geq 7.5\%$ . A new study suggests that using the new guidelines, and hence the NS, more patients are treated with statins. (9) This research, however, explored the American population, and therefore the results are not necessarily extrapolated to our country.

Finally, there is evidence that incorporating the presence of carotid atherosclerotic plaque (CAP) to a model consisting of traditional risk factors improves the prediction of cardiovascular events. (10) Even though the last European guidelines on cardiovascular prevention include CAP in risk stratification, (11) surprisingly, these have not been incorporated in the last American recommendations. (8) The optimal cut-off point (OCP) that best discriminates between subjects with or without CAP in several risk scores has been previously published. (12, 13) A similar analysis with the NS has not been reported.

Therefore, the aims of the study were: 1) To stratify cardiovascular risk in a primary prevention population using four risk scores, including the NS; 2) To estimate the concordance between these risk scores; 3) To describe the prevalence of CAP in the different risk strata according to the different scores; 5) To establish the NS OCP discriminating between subjects with or without CAP evidence.

## METHODS

A multicenter, descriptive, cross-sectional study was performed on consecutive samples obtained in the cardiovascular prevention outpatient clinics of six cardiology centers in the Autonomous City of Buenos Aires and Greater Buenos Aires.

Subjects aged between 20 and 79 years (age limit allowing the NS risk calculation) were included in the study. Exclusion criteria were: 1) previous cardiovascular disease; 2) history of diabetes mellitus and 3) prior hypolipidemic therapy.

## Definition of variables

Four risk scores were calculated:

1. The FS for coronary events using the third National Cholesterol Education Program (NCEP) expert panel report on elevated blood cholesterol detection, assessment and treatment in adults (Adult Treatment Panel III - ATP III), defining low, moderate and high risk as values  $< 10\%$ , between  $10\%$  and  $19\%$  and  $\geq 20\%$ , respectively. (14) The appropriateness of statin treatment was established (absolute or optional indication) following ATP III guidelines (according to estimated risk and LDL-C level).

2. The ES for fatal events, using the specific score corresponding to low risk countries. The choice of this score was arbitrary, based on the fact that most Argentine immigrant population comes from those countries. Risk  $< 1\%$ , between  $1$  and  $4.9\%$ ,  $5$  and  $9.9\%$  or  $\geq 10\%$  was classified as low, moderate, high or very high, respectively. Definite and optional (suggested) statin indications (taking into account estimated risk and LDL-C level) were analyzed following European cardiovascular prevention guidelines. (11)

3. The WHOS, with values  $< 10\%$ , between  $10$  and  $19\%$ ,  $20$  and  $29\%$  or  $\geq 30\%$  defining low, moderate, high or very high risk, respectively. (7) Statin indication according to the WHO (patients with  $\geq 20\%$  risk,  $> 40$  years old and with LDL-C  $> 3$  mmol/L or patients with  $\geq 30\%$  risk) was analyzed.

4. The NS used by the last American guidelines for cholesterol management. (8) A "definite indication for statin therapy" was defined if LDL-C was  $\geq 190$  mg/dL, or for 40 to 75 year-old patients with LDL-C between 70 and 189 mg/dL and risk  $\geq 7.5\%$ . "Optional indication for statin therapy" was established for risk between  $5\%$  and  $7.4\%$  or for any other condition supported by the guidelines.

Ultrasound was used to noninvasively quantify CAP presence. Plaque characterization had to fulfill the following requirements (ARIC group definition): 1) abnormal wall thickness (intima-media thickness  $> 1.5$  mm), 2) abnormal structure (protrusion towards the lumen, loss of alignment with the adjacent wall) and 3) abnormal wall echogenicity. Carotid atherosclerotic plaque prevalence was compared between the different risk strata in the different scores used.

## Statistical analysis

A ROC (receiver operating characteristic) analysis was conducted to determine the area under the curve assessing the NS accuracy to discriminate between subjects with or without CAP. The Youden index [maximum vertical distance between the ROC curve and the line of statistical chance (CJ point)] was used to determine the score OCP. Variable normality was explored analyzing the mean, standard

deviation, median, skewness, kurtosis and histogram, and using the Shapiro-Wilk test. Continuous data were compared between groups using the t test for normal distribution or the Mann-Whitney-Wilcoxon test for non-normal distribution. The analysis of categorical data was performed using the chi-square test.

The correlation between the FS, the ES and the WHOS was analyzed to classify patients into low, moderate or high/very high risk strata, using the Fleiss kappa index. Mild or poor, acceptable or discrete, moderate, significant or almost perfect agreement was defined if the kappa value was < 0.20, between 0.21 and 0.40, 0.41 and 0.60, 0.61 and 0.80 and 0.81 and 1, respectively. (15) A chi-square test for homogeneity was performed to compare between kappa values.

Continuous variables were expressed as mean  $\pm$  standard deviation, and categorical variables as percentages. A two-tailed p value < 0.01 was considered as statistically significant. STATA 11.1 and 3.1 EPIDAT software packages were used for statistical analysis.

### Ethics considerations

The study was conducted following the recommendations in medical research suggested by the Declaration of Helsinki, Guidelines for Good Clinical Practice and valid ethical regulations.

The protocol was reviewed and approved by the Ethical Board of each institution.

### RESULTS

A total of 772 patients (mean age  $52 \pm 11$  years, 66% women) were included in the study. Average body mass index was  $26.9 \pm 4.5$  and mean cholesterol, LDL-C, HDL-C and triglyceride values were  $219 \pm 45$  mg/dL,  $142 \pm 43$  mg/dL,  $50 \pm 14$  mg/dL and  $138 \pm 118$  mg/dL, respectively. Thirty six percent of patients were receiving antihypertensive treatment and 20.5% were active smokers.

### Risk stratification

Average FS, ES and NS values were  $6.1\% \pm 6.5\%$ ,  $1.7\% \pm 2.1\%$  and  $6.9\% \pm 6.9\%$ , respectively.

According to the FS, 76.8%, 17.5% and 5.7% of the population was classified at low, moderate or high risk. Applying the ES, 50.9%, 40.2%, 7.4% and 1.4% of patients were stratified as having low, moderate, high or very high risk, respectively. Finally, using the WHOS, 91.7%, 6.3%, 0.9% and 1.1% were considered at low, moderate, high or very high risk, respectively.

Total and by gender risk strata according to the different scores are shown in Table 1.

### Concordance between risk scores

Concordance between the FS, the ES and the WHOS was evaluated to classify patients in three groups: low, moderate, or high/very high risk. Overall, the agreement was poor between the three scores (kappa 0.14), being worse in women than in men (kappa 0.06 vs. 0.17,  $p = 0.002$ ). Concordance was discrepant to classify subjects at high/very high risk (kappa = 0.21) and poor when evaluating patients at low risk (kappa = 0.18) or intermediate risk (kappa = 0.08). The concordance between the FS and the ES was better in

men (kappa 0.47 vs. 0.08,  $p < 0.001$ ), while the concordance between the FS and the WHOS (kappa 0.27 vs. 0.08,  $p = 0.0001$ ) and between the WHOS and the ES (kappa 0.15 vs. 0.08,  $p = 0.05$ ) was better in women. The agreement between two or more scores in the overall and by gender population can be seen in Table 2.

### Recommendation for the use of statins:

According to the ATP III and based on the FS, the use of statins was unquestionably recommended in 23.6% of cases. When there was no absolute recommendation, 23.5% of patients had an optional indication.

When the European guidelines were applied using the ES, statins were immediately recommended only in 7% of cases, although their indication was suggested in 50% of patients who did not meet this recommendation.

Following the WHO recommendations, use of their specific score indicated use of statins in only 3% of cases.

Finally, considering the new American guidelines, 33% of the population had absolute indication for statin therapy. Eighteen percent of the population who did not apply for this indication, had a relative or optional recommendation.

The proportion of patients with complete or optional recommendation, by gender and age group (> or < 60 years), are shown in Table 3.

### Prevalence and characteristics of patients with carotid atherosclerotic plaque

Subjects with CAP were older ( $57.7 \pm 8.7$  vs.  $49.8 \pm 11.3$  years,  $p < 0.01$ ), evidenced a non-significant propensity to have higher cholesterol ( $224.3 \pm 46.3$  mg/dL vs.  $217.5$  mg/dL,  $p = 0.05$ ), had greater body mass index ( $27.9 \pm 4.4$  vs.  $26.3 \pm 4.5$ ,  $p < 0.001$ ), and higher

**Table 1.** Cardiovascular risk stratification according to different scores

Risk score	Total population n=772	Men n=342	Women n=430
FS, %			
Low	77	56	94
Moderate	17	32	6
High	6	12	1
ES, %			
Low	51	45	56
Moderate	40	43	38
High	7	10	5
Very high	2	2	1
WHOS			
Low	92	92	92
Moderate	6	6	6
High	1	0.3	1.5
Very high	1	1.7	0.5

FS: Framingham score. ES: European score. WHOS: Score recommended by the World Health Organization.

prevalence of smoking (31.1% vs. 15.09%,  $p < 0.001$ ) and anti-hypertensive treatment (52.8% vs. 28.4%,  $p < 0.001$ ) than patients without CAP.

Mean FS, EP and NS were significantly higher in patients with CAP [ $9.9\% \pm 7.3\%$  vs.  $4.3\% \pm 5.1\%$  ( $p < 0.001$ ),  $2.8\% \pm 2.6\%$  vs.  $1.1\% \pm 2.6\%$  ( $p < 0.001$ ) and  $10.5\% \pm 7.9\%$  vs.  $4.9\% \pm 5.4\%$  ( $p < 0.001$ ), respectively].

Overall, the prevalence of CAP was 33%, being greater in the higher risk strata, in all the scores evaluated (Figure 1). Analyzing the NS, the incidence of CAP was 19%, 38% and 51% in groups presenting risk  $< 5\%$ , between 5% and 7.5% and  $\geq 7.5\%$ , respectively.

When evaluating only the population with CAP, 55% of patients should receive statins (collectively considering absolute or optional recommendations) applying the FS, 73% using the ES or the NS and only 6% applying the WHOS.

**Discrimination of NS to detect carotid atherosclerotic plaque**

The area under the NS curve to discriminate subjects with or without CAP was 0.77 (95% CI 0.73-0.80) and the OCP was 5.2% (sensitivity 71%, specificity 70%, Yunden 0.41). The value of 7.5% proposed by the guidelines as a limit to definitively use statins to treat patients showed lower discrimination power (sensitivity 56%, specificity 82%, Yunden 0.38). Figure 2 shows the area under the NS curve, the OCP and the explored points.

**DISCUSSION**

Accurate cardiovascular risk stratification can be a complex task. Currently, there is no a score specifically designed for our country, and consequently risk func-

tions developed in other countries are usually used.

A primary prevention population was evaluated in the present study. Most of the population was classified at low risk upon application of the three risk scores. This finding was more marked when the WHOS was used and less defined when the ES was applied. Also, when the latter was used, more subjects were classified at intermediate risk. Our findings are consistent with previously published data in our country, where most of the primary prevention population was classified at low risk. (12, 16)

In our study the agreement between the different scores was generally poor. It was discreet in the high-risk level and poor in the categories of low or moderate risk. Moreover, the agreement was lower in females. Overall, our findings are consistent with previous data. For example, in a German study, the number of patients classified at high, moderate or low risk differed substantially by applying different scores (PROCAM, FS and ES). (17) Similarly, in an analysis carried out in Spain, the overall concordance between the FS and the REGICOR (adjusted for the Spanish population) was very poor ( $\kappa = 0.06$ ), being moderate in the low risk population ( $\kappa = 0.53$ ). (18) In our country, a study that stratified risk in a population of Bahía Blanca, showed moderate levels of agreement between the FS and the ES ( $\kappa = 0.49$ ). (16) Different populations probably explain the difference with the present study, where the population showed a lower body mass index and a lower proportion of men and smoking compared with the Bahía Blanca study.

In the study, patients at higher risk showed higher prevalence of CAP. However, this prevalence was not negligible in low-risk subgroups. Our findings are consistent with previously reported data. In a study in Mexican Americans, 32% and 50% of the population classified as having low or moderate risk by the FS presented an “abnormal” carotid Doppler analysis (intima-media thickness  $> 75$ th percentile or presence of CAP). (19) Similarly, in postmenopausal women stratified as presenting low risk by the FS and the WHOS, the prevalence of CAP was 27% and 26%, respectively. (13)

On the other hand, our study showed a higher prevalence of CAP compared with reports analyzing the general population. For example, one study re-

**Table 2.** Concordance between risk scores

Comparison	Total population Kappa (SE)	Men Kappa (SE)	Women Kappa (SE)
FS and ES	0.30 (0.03)	0.47 (0.04)	0.08 (0.02)
FS and WHOS	0.13 (0.03)	0.08 (0.03)	0.27 (0.04)
ES and WHOS	0.12 (0.02)	0.08 (0.02)	0.15 (0.03)
Combined	0.14 (0.03)	0.17 (0.03)	0.06 (0.02)

SE: Standard error. FS: Framingham score. ES: European score. WHOS: Score recommended by the World Health Organization.

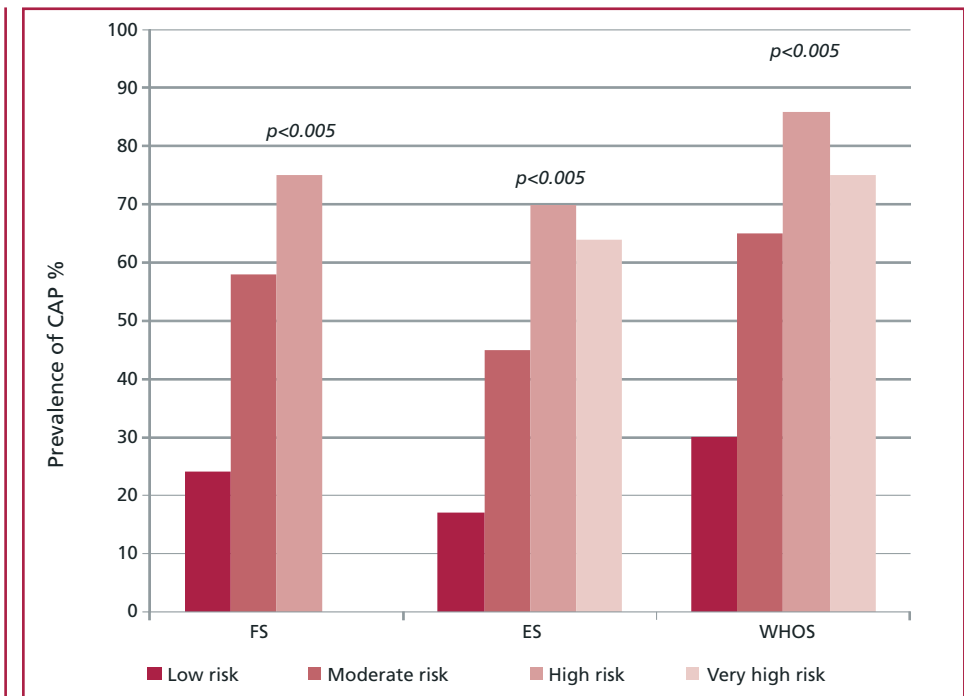
Risk score	Men	Women	p	Men	Women	p
<b>Absolute indications</b>						
FS, %	35.8	14.2	$< 0.001$	21.9	26.9	0.20
ES, %	8.8	5.6	0.08	2.0	27.3	$< 0.001$
WHOS, %	3.9	2.1	0.15	2.9	3.5	0.74
NS, %	45.5	23.2	$< 0.001$	24.9	62.1	$< 0.001$
<b>Optional indications*</b>						
FS, %	28.4	22.4	0.02	23.3	22.9	0.93
ES, %	56.5	45.5	$< 0.05$	44.0	70.9	$< 0.001$
WHOS, %	-	-	-	-	-	-
NS, %	20.3	17.2	0.23	14.5	47.3	$< 0.001$

\*In patients without absolute indication.

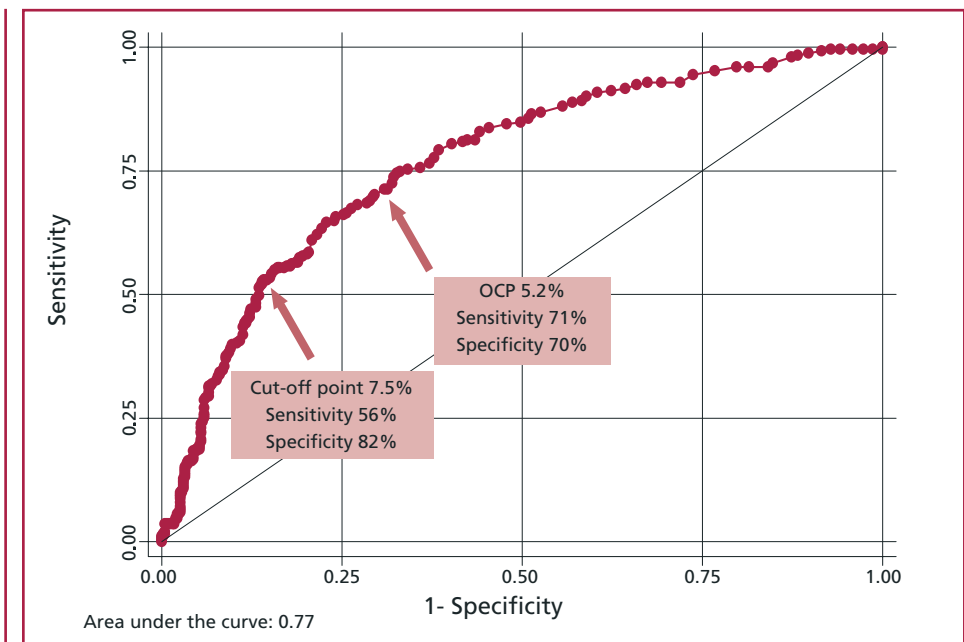
FS: Framingham score. ES: European score. WHOS: Score recommended by the World Health Organization.

**Table 3.** Absolute and optional statin indications according to the different scores applied, by gender and age.

**Fig. 1.** Prevalence of carotid atherosclerotic plaque (PAC) according to risk strata. FS: Framingham score. ES: European score. WHOS: Score recommended by the World Health Organization.



**Fig. 2.** Discrimination capacity of the new American risk score between subjects with or without carotid atherosclerotic plaque (ROC analysis). Arrows show the optimal cut-off point (OCP) and the 7.5% cut-off point recommended by the guidelines as therapeutic limit.



ported that the prevalence of CAP in the categories of low, moderate and high risk (according to the FS) was 11.3%, 37.1% and 68.9%, respectively. (20) This is expected, since patients attending the clinic have a higher prevalence of risk factors than the general population.

Application of most scores showed that nearly half of the population had absolute or relative indication for statins (FS: 42%, ES: 46% and NS: 45%). An exception worth noting is that using the WHOS, statins should be indicated in only 3% of the population. Substantial differences in the use of statins were also reported in an Italian study evaluating seven cardiovas-

cular risk scores (from 1.1% to 17.5%). (21)

A recent study showed that compared with the classical FS, the NS increases the proportion of subjects treated with statins from 37.5% to 48.6%. (9) The results were most striking in subjects older than 60 years. Except for the WHOS, and considering the total population, our study showed no major differences in the percentage of patients to be treated with statins using any score. However, in agreement with the aforementioned study, use of statins would also increase in subjects > 60 years not only applying the NS (from 25% to 62%, considering absolute indications) but also using the ES (from 2% to 27%, taking into ac-

count absolute indications). Finally, it should be noted that both the FS as the NS would indicate significantly more statins in men than in women.

It is interesting to point out that analyzing the CAP population, the ES and the NS were the scores that recommended statin therapy to the largest proportion of patients (73%). On the other hand, based on the WHOS, 94% of subjects with CAP would not receive statins.

The OCP of several scores to discriminate between subjects with or without CAP has been previously assessed. For example, the OCP of the FS at 30 years based on the lipid profile was 26%. (12) Similarly, in another study conducted in our country, the OCP to detect CAP in a group of postmenopausal women was 3%. (13) In our study, the OCP of the NS was 5.2%. This finding, though speculative, is interesting because it is nearer to 5% and not to 7.5% which is the value the new guidelines propose as a limit to indisputably treat with statins. Perhaps these results suggest that the score should be calibrated in our population, to determine whether the cut-off points suggested by the new guidelines are adequate for our region.

Research for risk factors and proper risk stratification are rare in Latin America. (22) Knowledge of the application of different risk scores in our population could favor the difficult task of estimating cardiovascular risk in our patients.

## CONCLUSIONS

Our findings showed that the population was mostly classified at low risk by all scores, with poor agreement between them. Risk stratification and use of statins varied according to the risk function used. Understanding the relationship between presence of CAP and scores could improve the estimation of risk in our population.

## Conflicts of interest

None declared.

(See authors' conflicts of interest forms in the web / Supplementary Material).

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