ORIGINAL ARTICLE

Estimation of Cardiovascular Risk and Detection of Subclinical Carotid Artery Atheromatosis in Middle-Aged Postmenopausal Women

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ABSTRACT

Background
Cardiovascular disease in women increases after menopause. Traditional risk scores underestimate the risk in postmenopausal women. The diagnosis of carotid atherosclerotic plaque (CAP) could improve risk stratification.

Objectives
The aim of the study was: 1) to estimate cardiovascular risk in middle-aged postmenopausal women in primary prevention. 2) To find CAP prevalence. 3) To assess the precision of risk scores used to detect CAP.

Methods
The level of agreement between the 10-year Framingham risk score (10-FRS) and the score recommended by the World Health Organization (WHO) was assessed. Ultrasound was used to determine CAP occurrence. A ROC analysis was performed.

Results
The study included a total of 334 women with mean age 57 ± 5 years. According to the 10-FRS and the WHOS, 96% and 91% of the population were respectively classified as "low risk". A fair level of agreement between both scores was found (kappa 0.31). CAP occurred in 29% of cases. Score estimated risk correlated with CAP prevalence. Women with CAP presented higher incidence of hypertension and smoking, evidencing a more frequent "metabolic" pattern than women without CAP. The area under the curve of the 10-FRS to detect CAP was 0.79 (95% CI 0.73-0.84), with an optimal cut-off point ≥ 3%.

Conclusions
In this population, mostly classified as low risk, there was considerable CAP prevalence. A carotid ultrasound might help to stratify cardiovascular risk when the 10 FRS is ≥ 3%.

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Key words > Postmenopausal women - Cardiovascular risk evaluation - Atherosclerotic plaque.

Abbreviations >

CAP	Carotid atherosclerotic plaque	**LDL-C**	Cholestrol carried by low density lipoproteins
10-FRS	10-year Framingham risk score	**WHO**	World Health Organization
HDL-C	Cholestrol carried by high density lipoproteins	**WHOS**	World Health Organization score

INTRODUCTION
The incidence of cardiovascular disease in premenopausal women is significantly lower compared to men of similar age. (1, 2) After menopause, the incidence is comparable between both sexes and can even be inverted in elderly people. (3, 4) The lack of protection provided by estrogens was the main mechanism proposed to explain such findings. The anti-atherogenic and antithrombotic effect of estradiol, which is the main estrogen synthesized during premenopause, was thought to be responsible for reducing the progression of the atherosclerotic process and delay the development of cardiovascular events in women compared to men. (5, 6) However, hormone replacement therapy has not

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proved to reduce cardiovascular events in clinical trials (7) and some models suggest that cardiovascular mortality in women increases with age in an exponential fashion with no clear acceleration in menopause. (8) Changes in the traditional risk factors and increased prevalence of the metabolic syndrome after menopause are other pathophysiological mechanisms proposed to explain the change in the incidence of cardiovascular disease in postmenopausal women. (9, 14)

The traditional methods for the evaluation of cardiovascular risk have limitations and might underestimate the risk in postmenopausal women. In medical practice, and even under the presence of several risk factors, most women under 75 years (particularly those < 65 years) are considered at "low cardiovascular risk" by the traditional risk scores. (15-16)

The incorporation of carotid intima-media thickness and the presence or absence of carotid artery plaque (CAP) to a model which includes traditional coronary risk factors improves the prediction of cardiovascular events in men and women. (17) In this context, the current guidelines recommend the use of a new risk score cutoff point at 10 years (>10%) for defining high risk in women. (18)

Considering the aforementioned issues, the goals of the present study were: 1) to estimate cardiovascular risk in a population of postmenopausal middle-aged women in primary prevention using risk scores; 2) to analyze the prevalence of CAP and its association with risk scores; and, 3) to calculate the accuracy of risk scores to detect CAP and to determine the optimal cut off point to discriminate between women with or without evidence of CAP.

METHODS

We conducted a cross-sectional multicenter descriptive study of consecutive samples obtained in the outpatient clinic of cardiovascular prevention (see Appendix).

Inclusion criteria were women ≤ 65 years with ≥ 2 years after their last menstrual period.

Exclusion criteria were history of cardiovascular disease (myocardial infarction, unstable angina, chronic stable angina, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke, peripheral vascular disease, or disease of the aorta or its branches), 2) diabetes mellitus, 3) previous treatment with lipid lowering agents, and 4) hormone replacement therapy.

Cardiovascular risk was estimated by using two risk charts: 1) the 10-year Framingham risk score (10-FRS) for fatal or non-fatal coronary events used by the Third Report of the Expert Panel of the National Cholesterol Education Program on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III), which defined three risk categories: low (<10%), moderate (between 10% and 19%) and high (≥ 20%) (19); 2) the WHO score (WHOS) recommended for Argentina, which defines four risk categories: low (< 10%), moderate (between 10% and 19%), high (between 20% and 29%) and very high (≥ 30%). (20) Finally, two categories were used to divide the population into "low risk" (< 10%) and "no low risk" (≥10%).

The carotid arteries were explored non-invasively to detect CAP using two-dimensional ultrasound with an ultrasound scanner with a linear probe. The presence of CAP was defined as: 1) abnormal wall thickness (defined as 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. Laboratory tests and carotid Doppler ultrasound were performed at each participating center. The prevalence of CAP was compared among the different risk categories. A ROC (receiver operating characteristic) curve was built and the area under the curve was determined to ascertain how accurately the 10-FRS discriminates between subjects with or without CAP. The Younden index, which corresponds to the maximum vertical distance between the ROC curve and the statistical chance line (CJ point), was used to determine the optimal cutoff point. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Continuous data between two groups were analyzed using the t test for normal distributions or the Wilcoxon Mann-Whitney test for non-normal distributions. Categorical data were analyzed with the chi-square test. Cohen's weighted kappa index was used to evaluate the agreement between two classifications. Continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. A p value < 0.05 was considered statistically significant.

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

RESULTS

Risk stratification in the population

A total of 334 women with mean age 57 ± 5 years were included in the study. The baseline characteristics of the population are described in Table 1.

The 10-FRS identified 96% of the population as having low risk and only 4% as facing moderate risk. This risk score did not categorize any patient as high risk. According to the WHOS, 91%, 8% and 1% of women had low, moderate or high risk, respectively. Five patients stratified by the 10-FRS as "no low risk" were categorized as "low risk" by the WHOS. On the other hand, 22 women categorized as "no low risk" by the WHOS were stratified as "low risk" by the 10-FRS. The agreement between both scores in categorizing the population as "low risk" or "no low risk" was fair (kappa 0.31).

Prevalence of CAP and its association with risk scores

The prevalence of CAP in the population was 29% (n = 98). The 10-FRS was significantly higher in women with CAP (4.9 ± 3.6% vs. 2.1 ± 1.8%, p<0.0001) compared to women without CAP. Table 2 displays the characteristics of the population according to the presence or absence of CAP. The prevalence of CAP in women categorized as low risk by the 10-FRS and the WHOS was 27% and 26%, respectively. Figure 1 shows the prevalence of CAP according to "low risk" or "no low risk" categories using the 10-FRS and the WHOS.

Both scores classified more women with CAP in the moderate/high risk categories compared to women without CAP (10-FRS: 10% vs. 1%, p<0.001; WHOS:

Table 1. Characteristics of the population

	n=334
Continuous variables, mean (SD)	
Age, years	57 (5)
Systolic blood pressure, mm Hg	124 (15)
Total cholesterol, mg/dl	225 (39)
LDL-C, mg/dl	145 (37)
HDL-C, mg/dl	57 (14)
Triglycerides, mg/dl	119 (62)
Body mass index, kg/m2	25.8 (4.4)
Blood glucose, mg/dl	98 (13)
Maximum intima-media thickness, mm	1.09 (0.47)
Categorical variables, n (%)	
Current smokers	78 (23)
Antihypertensive treatment	91 (27)
Beta blockers	20 (22)
Calcium channel blockers	32 (35)
Diuretics	30 (33)
ACEI	33 (36)
ARB	34 (38)
Two drugs	35 (38)
Three drugs or greater	12 (13)
Family history*	84 (25)
10-year Framingham risk score	
Low risk	322 (96)
Moderate risk	12 (4)
High risk	0 (0)
WHO score	
Low risk	305 (91)
Moderate risk	25 (8)
High or very high risk	4 (1)

*Family history of early cardiovascular disease (< 55 years in men and < 65 years in women in first-degree relatives). SD: Standard deviation. LDL-C: Cholesterol carried by low-density lipoproteins. HDL-C:Cholesterol carried by high-density lipoproteins. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; WHO: World Health Organization.

19% vs. 4%, p<0.001). However, when only the subpopulation with CAP (n = 98) was analyzed, most were initially classified as low cardiovascular risk by both scores (10-FRS 90%, WHOS 81%).

ROC analysis

The area under the ROC curve using the 10-FRS to detect CAP was 0.79 (95% CI 0.73-0.84, Younden index 0.46) and the optimal cut off point was ≥ 3% (sensitivity 71%, specificity 75%, positive predictive value 52%, negative predictive value 86%). A higher sensitivity cut off point was explored (≥ 2%; sensitivity 87%), with a negative predictive value of 91%. The traditional cut off point used to categorize patients as low risk (< 10%) showed a sensitivity of 10% and a specificity of 99%. Figure 2 shows the ROC curve, the optimal cutoff point, the exploratory cutoff point for high sensitivity and the traditional cut off point of 10%.

DISCUSSION

Cardiovascular disease is the leading cause of death in women, with a marked increase after menopause. The traditional methods for the estimation of cardiovascular risk have limitations when applied to women. In our study, we have calculated cardiovascular risk using two functions: the 10-FRS, the most commonly used among our physicians, and the WHOS recommended for our country. After using the 10 FRS and the WHOS, 96% and 91% of the population, respectively, was categorized as low risk. These results are consistent with those reported by other publications. For example, the analysis of the baseline risk in some clinical trials showed that the prevalence of women with 10-FRS > 10% was only 44%. (21)

Therefore, the development of more efficient predictive tools is needed, considering that most cardiovascular events occur in populations with low to moderate risk (22). The diagnosis of subclinical atherosclerosis by ankle-brachial index measurement, detection of CAP by ultrasound or estimation of coronary artery calcium or aortic calcium by computed tomography scan is an independent predictor of new coronary events. (23-26) Prevalence of subclinical atherosclerosis is significant, even analyzing low-risk populations. (27-28) Prevalence of CAP in postmenopausal women in our study was 29%, similar to that reported by previous publications. (29) Even more, this number is similar to the one reported by studies evaluating exclusively postmenopausal women of low-moderate risk (30) or very low risk. (31) In other words, one third of postmenopausal women categorized as low risk presented CAP in our study. This result provides a great opportunity for implementing preventive measures, considering that these patients should be recategorized as "high risk".

Women with CAP were older, had more prevalence of hypertension and current smoking, higher plasma levels of cholesterol and LDL-C and showed a "metabolic" pattern (higher body mass index and triglycerides and lower HDL-C levels) compared to women without CAP. Although both scores stratified more women with CAP than without CAP as having moderate risk, none of the patients with CAP were categorized as high risk according to the 10-FRS and the WHOS categorized only two of them as high risk. The high prevalence of CAP in women with risk > 10% (83% and 66% by applying 10-FRS and WHOS, respectively, strengthens the recommendation provided by the new guidelines on cardiovascular prevention in women of considering them at "high risk".

In our study, the area under the ROC curve for the 10-FRS showed good discriminatory power between women with or without CAP, and the optimal cut off point ≥ 3% had acceptable sensitivity and specificity, with high negative predictive value. A higher sensitivity cut off point (≥ 2%), further increases the negative predictive value. These cut off points are far lower than those commonly used to define "low

	Without CAP (n = 236)	With CAP (n = 98)	p
Continuous variables, mean (SD)			
Age, years	56±5	58±5	0.03
Systolic blood pressure, mm Hg	122±14	129±15	<0.001
Total cholesterol, mg/dl	221±38	237±39	<0.01
LDL-C, mg/dl	141±36	154±37	<0.05
HDL-C, mg/dl	58±14	54±14	<0.05
Triglycerides, mg/dl	107±51	148±76	<0.001
Body mass index, kg/m2	25±4	27±5	<0.001
Blood glucose, mg/l	97±12	99±11	0.14
Mean intima-media thickness, mm	0.88±0.19	1.68±0.54	<0.001
Categorical variables, n (%)			
Current smokers	39 (17)	39 (40)	<0.001
Antihypertensive treatment	53 (22)	38 (39)	<0.01
Family history*	56 (24)	28 (29)	0.35
10-year Framingham risk score			
Low risk	234 (99)	88 (90)	<0.001
Moderate risk	2 (1)	10 (10)	
High risk	0 (0)	0 (0)	
WHO score			
Low risk	226 (96)	79 (81)	<0.001
Moderate risk	8 (3)	17 (17)	
High or very high risk	2 (1)	2 (2)	

*Family history of early cardiovascular disease (< 55 years in men and < 65 years in women in first-degree relatives). CAP: Carotid artery plaque. SD: Standard deviation.LDL-C: Cholesterol carried by low-density lipoproteins. HDL-C:Cholesterol carried by high-density lipoproteins. WHO: World Health Organization.

Table 2. Patient baseline characteristics

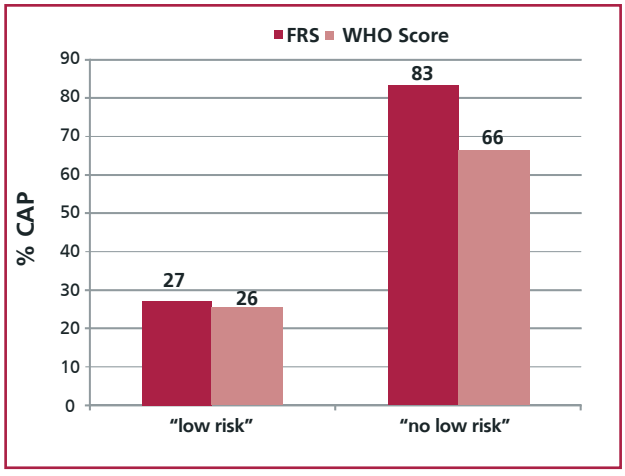

Fig. 1. Prevalence of CAP according to "low risk" or "no low risk" categories using the 10-FRS and the WHO score. CAP: Carotid artery plaque; 10-FRS: 10-year Framingham risk score; WHO: World Health Organization.

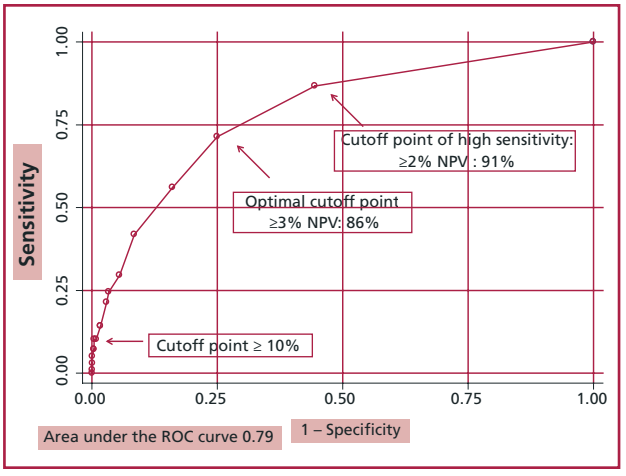

Fig. 2. Accuracy of the Framingham risk score to detect carotid atherosclerotic plaque. Arrows indicate the optimal cut off point and the exploratory cut off point for high sensitivity. The black arrow indicates the traditional cutoff point to determine "low" or "no low" risk. ROC: receiver operating characteristic; NPV: Negative predicted value.

risk" (<10%). In fact, the sensitivity of the 10-FRS cut off point to detect CAP was extremely low.

Limitations

The diagnosis of postmenopause was clinical (the limit of 2 years since the last menstruation was arbitrary) and not based on laboratory tests (determination of hormone levels)

A selection bias cannot be excluded as patients attending a cardiovascular prevention outpatient clinic are more likely to be ill and do not necessarily represent the general population.

In our study, we used the definition of CAP considered by the ARIC group. Changing the definition of CAP might modify our results. Other measurements, as intima-media thickness, indicators of vascular function or plaque characteristics were not considered for this analysis.

Clinical implications

Awareness of CAP prevalence in a population of postmenopausal women mostly categorized as being at "low risk", and recognizing the limitations of the tools commonly used to obtain such categorization might improve the strategies in primary prevention by individually adjusting cardiovascular risk in women. For example, considering that the average LDL-C level in the population is 145 mg/dl, optimized risk stratification might reconsider the prescription of statins in an important proportion of women. In addition, as the risk of stroke is greater, blood pressure control might be intensified in women with subclinical atherosclerosis.

Finally, the impact on risk prediction to make a echodoppler in patients with certain traditional score value is speculative and should be investigated in studies specifically designed for this.

CONCLUSIONS

In this group of postmenopausal women, the diagnosis of CAP was prevalent despite that most of them were categorized as low risk patients. The likelihood of subclinical carotid artery atherosclerosis is low, with a 10 FRS < 3% (even < 2%) and thus there is no need of making additional tests to adjust cardiovascular risk. In women with a 10-FRS ≥ 3%, the information provided by carotid Doppler ultrasound might improve cardiovascular risk stratification in this particular group of patients.

RESUMEN

Estimación del riesgo cardiovascular y detección de ateromatosis carotídea subclínica en mujeres posmenopáusicas de mediana edad

Introducción

La incidencia de enfermedad cardiovascular en la mujer aumenta luego de la menopausia. Los puntajes de riesgo tradicionales subestiman el riesgo en la mujer posmenopáusica. El diagnóstico de placa aterosclerótica carotídea (PAC) podría mejorar la estratificación del riesgo.

Objetivos

1) Estimar el riesgo cardiovascular en mujeres posmenopáusicas de mediana edad en prevención primaria. 2) Conocer la prevalencia de PAC. 3) Calcular la precisión de los puntajes de riesgo para detectar PAC.

Material y métodos

Se calcularon el puntaje de Framingham a 10 años (PF10) y el puntaje recomendado por la Organización Mundial de la Salud (POMS), evaluando la concordancia entre ellos. Se determinó la prevalencia de PAC mediante ultrasonido. Se realizó un análisis ROC.

Resultados

Se incluyeron 334 mujeres (edad 57 ± 5 años). El 96% y el 91% de la población se clasificó como de "riesgo bajo" según el PF10 y el POMS, respectivamente. La concordancia entre los dos puntajes fue regular (kappa 0,31). La prevalencia de PAC fue del 29%. Se observó una correspondencia entre el riesgo estimado por los puntajes y la prevalencia de PAC. Las mujeres con PAC presentaron una prevalencia mayor de hipertensión arterial y tabaquismo, mostrando más frecuentemente un patrón "metabólico" que las mujeres sin PAC. El área bajo la curva del PF10 para detectar PAC fue de 0,79 (IC 95% 0,73-0,84), siendo el punto de corte óptimo ≥ 3%.

Conclusiones

En esta población clasificada en su mayoría como de riesgo bajo, la prevalencia de PAC fue considerable. Ante un PF10 ≥ 3%, la solicitud de una ecografía carotídea podría optimizar la estratificación del riesgo cardiovascular.

Palabras clave > Mujeres posmenopáusicas - Evaluación de riesgo cardiovascular - Placa de ateroma

Conflicts of interest

Dr Cecilia Zeballos is a Medical Advisor at AztraZeneca Argentina. The other authors declare no conflicts of interest.

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APPENDIX

Participating centers

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Hospital Militar Campo de Mayo
Consultorio particular cardiológico de Luján
FLENI

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