ORIGINAL ARTICLE

CME

Significance of Subclinical Atherosclerosis in Cardiovascular Risk Assessment

Valor de la aterosclerosis subclínica en la determinación del riesgo cardiovascular

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ABSTRACT

Background: The current recommendation for risk stratification of the new ACC/AHA guidelines on cholesterol therapy to reduce atherosclerotic cardiovascular risk questions the usefulness of subclinical atherosclerosis detection in primary prevention.
Objectives: The aim of this study was to analyze the prevalence of subclinical atherosclerosis assessed by carotid echocardiography in the different risk groups according to the new guidelines, and to evaluate the prevalence of subclinical atherosclerosis in the different subgroups when a sub-stratification based on the number of risk factors is added.
Methods: Consecutive primary prevention patients were selected. Patients with a history of diabetes and/or coronary artery disease and/or peripheral vascular disease were excluded from the study. Subclinical atherosclerosis was defined as the presence of one or more atherosclerotic plaques detected by carotid Doppler echocardiography.
Results: Five hundred and forty one patients were analyzed; 243 (45%) were stratified as low risk, 100 (18%) as intermediate risk and 198 (37%) as high risk. The prevalence of plaque (subclinical atherosclerosis) was 12% (95% CI 9-17) in the low risk group, 23% (95% CI 16-32) in the intermediate risk group and 41% (95% CI 34-48) in the high risk group (p<0.001). When analyzing the different subgroups, the prevalence of subclinical atherosclerosis was 30% (95% CI 20-43) in the intermediate risk patients with two or more risk factors; however, in the subgroup with 0 to 1 risk factors, the prevalence was 14% (95% CI 6-27) (p<0.05).
Conclusions: Subclinical atherosclerosis assessment added to the number of risk factors can identify subjects with different risks beyond the stratification established by the new American guidelines, which can be useful when deciding individual therapeutic management.

Key words: Primary Prevention - Atherosclerosis - Plaque, Atherosclerotic - Risk Factors

RESUMEN

Introducción: La recomendación actual para la estratificación de riesgo de las nuevas guías ACC/AHA sobre tratamiento del colesterol para la reducción del riesgo cardiovascular aterosclerótico plantea un interrogante sobre la utilidad de la detección de aterosclerosis subclínica en prevención primaria.
Objetivos: Analizar la prevalencia de aterosclerosis subclínica evaluada con eco carotídeo en los diferentes grupos de riesgo según las nuevas guías. Analizar la prevalencia de aterosclerosis subclínicade los diferentes subgrupos cuando se agrega una subestratificación basada en el número de factores de riesgo.
Material y métodos: Se seleccionaron pacientes consecutivos de prevención primaria. Se excluyeron los pacientes con historia de diabetes y/o enfermedad coronaria y/o vascular periférica. Se definió aterosclerosis subclínicaa la presencia de una o más placas ateroscleróticas detectadas por eco-Doppler carotídeo.
Resultados: Se analizaron 541 pacientes, de los cuales 243 (45%) se estratificaron de riesgo bajo, 100 (18%) de riesgo intermedio y 198 (37%) de riesgo alto. La prevalencia de placa (aterosclerosis subclínica) fue del 12% (IC 95% 9-17) en el grupo de riesgo bajo, del 23% (IC 95% 16-32) en el de riesgo intermedio y del 41% (IC 95% 34-48) en el grupo de riesgo alto (p < 0,001). Al analizar los diferentes subgrupos, en los pacientes de riesgo intermedio con dos o más factores de riesgo se observó una prevalencia de aterosclerosis subclínicadel 30% (IC 95% 20-43); en cambio, en el subgrupo con 0 a 1 factor de riesgo, la prevalencia fue del 14% (IC 95% 6-27) (p < 0,05).
Conclusiones: La evaluación de la aterosclerosis subclínica sumada al número de factores de riesgo permite identificar a sujetos con diferentes riesgos, más allá de la estratificación de las nuevas guías americanas, lo cual puede ser de utilidad al momento de decidir la terapéutica individual.

Palabras clave: Prevención primaria - Aterosclerosis - Placa carotídea - Factores de riesgo

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Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association	NCEP-ATP III	National Cholesterol Education Program - Adult Treatment Panel III
SCA	Subclinical atherosclerosis		
HDL-C	Cholesterol carried by high density lipoproteins	P25-75	25-75 percentile
LDL-C	Cholesterol carried by low density lipoproteins	hs-CRP	High-sensitivity C-reactive protein
IMT	Intima –media thickness		

INTRODUCTION

The new 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on cholesterol therapy to reduce atherosclerotic cardiovascular risk in adults recommend the score based on an equation developed from a combined cohort of United States patients without atherosclerotic disease to predict the risk of an atherosclerotic cardiovascular event (nonfatal myocardial infarction, death from coronary heart disease, and fatal or nonfatal stroke) at 10 years. (1) The guidelines assign high risk to 40 to 75-year old patients with score≥7.5%, recommending the administration of moderate to high doses of statins without taking into account the assessment of subclinical atherosclerosis (SCA) by carotid echocardiography to stratify patients. Moreover, these guidelines indicate an intermediate risk group (score≥5% and<7.5%) with potential or "reasonable" indication of treatment with moderate doses of statins. These recommendations contrast with the classic approach based on risk factors according to previous guidelines of the National Cholesterol Education Program (NCEP-ATP III) in which patients in primary prevention were stratified according to the number of risk factors with the addition of the Framingham score at 10 years in patients with two or more risk factors. (2) There is evidence regarding the additional importance of SCA assessment on the prediction of cardiovascular risk (3, 4) and various prevention guidelines, including that of the Argentine Society of Cardiology (SAC), have mentioned the usefulness of determining SCA by carotid echocardiography to improve risk stratification in patients with moderate or intermediate initial risk. (5-8) As a result of these methodological changes, it is interesting to analyze stratification with the new ACC-AHA score, with the inclusion of additional risk factor assessment and detection of SCA by carotid echocardiography in a population of patients of our country.

METHODS

An observational, cross-sectional study was performed in patients progressively included in the cardiovascular prevention database of our institution. First-time primary prevention patients, aged between 40 and 75 years, with LDL cholesterol levels between 70 and 189 mg/dL, without pharmacological treatment at inclusion and who had completed clinical, biochemical and carotid echo-Doppler evaluation, were consecutively included in the study. All patients with history of diabetes and/or coronary heart disease and/or peripheral vascular disease were excluded from the study.
The primary endpoint was the analysis of SCA prevalence as-

sessed with carotid echo-Doppler in the different risk groups, according to the new 2013 ACC/AHA guidelines. The secondary endpoint was the analysis of SCA prevalence in the different subgroups when a sub-stratification is added based on the number of risk factors, according to NCEP-ATP III.

Patients were divided into three subgroups of absolute risk following the new American 2013 ACC/AHA guidelines' score: low-risk with score <5%, intermediate risk with score ≥5% and <7.5% and high risk with score ≥7.5%.

Subclinical atherosclerosis was defined as the presence of one or more atherosclerotic plaques detected by carotid echo-Doppler using the ARIC study criteria, (3) which take into account two of the three following conditions: a) increase of intima-media thickness (IMT) >1.5; b) abnormal shape (protrusion towards the lumen, loss of wall alignment; c) abnormal texture. The inflammatory response was assessed by the high-sensitivity C- reactive protein (hs-CRP) level measured by immunoturbidimetry, with a cut-off point >2 mg/dL or ≤2 mg/dL.

The population was sub-stratified according to the number of factors present: 0-1 or 2 or more risk factors. Using the NCEP-ATP III definitions, the risk factors considered were: smoking, hypertension (blood pressure ≥140/90 mmHg and/or antihypertensive treatment), HDL-C <40mg/dL (HDL-C ≥60 mg/dL was considered to subtract one risk factor), family history of early coronary heart disease and age (≥45 years in men and ≥55 years in women).

Demographic data and clinical history were retrospectively collected from patient prevention charts and clinical records. In all patients, biochemical analyses and carotid echocardiography studies were performed by the Central Laboratory and the Echocardiography Division of our institution.

Statistical analysis

The precision of the 541 patient sample to detect 25% prevalence of SCA in the overall population was <5% (between 3% and 4%). Mainly, descriptive statistics was performed. Categorical data are expressed as percentage of patients and 95% confidence intervals for the primary endpoints, and continuous variables as number of patients (N), mean and standard deviation (SD) for normal distribution and median with interquartile range [25-75 percentile (P25-75)] for non-normal distribution. Percentages were rounded to one decimal place. Inference statistics was used to perform bivariate analysis in the subgroup evaluation, applying the corresponding tests for quantitative or qualitative data with normal or non-normal distribution as appropriate, using a significance level of 5% with its corresponding adjust or "post-hoc" tests when multiple comparisons were performed. SPSS 9.0 software package was used for statistical analyses.

Ethical considerations

The study was approved by the Institutional Review Committee and was conducted following national regulations in force for observational studies.

RESULTS

A total of 1,164 consecutive subjects with a first visit to the Cardiovascular Prevention Service were systematically studied between January 2011 and January 2013. A total of 541/1,164 (46%) patients meeting the elegibility criteria defined in the study were selected.

Population characteristics

Among the 543 patients included in the study, 243 (45%, 95% CI 41-49%) were stratified as low risk, 100 (18%, 95% CI 15-22%) as intermediate risk and 198 (37%, 95% CI 33-41%) as high risk according to the score of the new American guidelines. In the analysis of the population characteristics summarized in Table 1, differences among the three risk subgroups were found in the initial analysis of all variables (age, male gender, total cholesterol, HDL-C, systolic blood pressure, hypertension treatment and smoking) defined in the new American guidelines' score, and also in the values of total cholesterol, LDL-C, triglycerides, blood glucose levels, apolipoprotein A1, apolipoprotein B and body mass index (see Table 1). A subsequent analysis indicated that the variables showing significant differences in the multiple comparisons performed among the three risk subgroups were age, male gender, prevalence of treated hypertension and systolic blood pressure, in all cases with $p \leq 0.001$ (see Table 1).

Prevalence of subclinical atherosclerosis and inflammatory response

Prevalence of SCA was 25% (95% CI 21-29) in the total population. When the three risk subgroups were analyzed according to the new American guidelines, the prevalence of plaque was 12% (95% CI 9-17) in the low risk group, 23% (95% CI 16-32) in the intermedi-

ate risk group and 41% (95% CI 34-48) in the high risk group ($p<0.001$) (Figure 1). In addition, the inflammatory response in the three risk subgroups analyzed by the prevalence of increased hs-CRP showed that the inflammatory response was 24% (95% CI 19-30) in the low risk group, 35% (95% CI 26-46) in the intermediate risk group and 40% (95% CI 32-48) in the high risk group ($p<0.01$). The analysis of hs-CRP indicated a non-normal distribution of the variable with a median of 1.1 mg/dL (P25-75: 0.5-2 mg/dL) in the low risk subgroup, 1.2 mg/dL (P25-75: 0.7-2.8 mg/dL) in the intermediate risk subgroup and 1.6 mg/dL (P25-75: 0.9-2.8 mg/dL) in high risk patients ($p<0.001$). In the overall population, subjects with SCA presented higher levels of hs-CRP [1.6 mg/dL (P25-75: 0.9-2.7 mg/dL)] compared with subjects without SCA [1.2 mg/dL (P25-75: 0.6-2.4 mg/dL)] ($p<0.05$).

Substratification according to risk factors

When the population was substratified according to the number of risk factors in subjects presenting 0-1 or 2 or more risk factors using the NCEP-ATP-III definitions, a significantly progressive increase in the prevalence of 2 or more risk factors was seen in the subgroups of patients at higher risk according to the new American guidelines, with a prevalence of 27%, 56% and 66% in the low risk, intermediate risk and high risk subgroups, respectively ($p<0.001$). The study of SCA prevalence as a variable in the subgroups of patients with 2 or more compared to 0-1 risk factors within each risk group (low, intermediate, high) according to the new American guidelines, showed that the prevalence of plaque in the intermediate subgroup of patients was significantly greater in patients with 2 or more risk factors: 30% (95% CI 20-43) compared with patients with 0-1 risk factors: 14% (95% CI 6-27)

Table 1. Population characteristics according to the 2013 ACC-AHA score

	Total Population (n=541)	Low Risk (n=243)	Intermediate Risk (n=100)	High Risk (n=198)
Age, years*	57±9	51±6	58±6	64±7
Male gender, %*	50	33	50	72
Treated hypertension, %*	62	44	65	82
Smoking, % ‡	9	5	10	13
Systolic blood pressure, mmHg*	124±15	118±14	124±12	132±14
Body mass index, kg/m2 ‡	27 ±4	26 ±5	27 ±4	27 ±4
Total cholesterol, mg/dL‡	208±32	205±31	215±31	208±32
LDL-C, mg/dL‡	130±28	127±26	137±27	129±29
HDL-C, mg/dL*	57±14	60±15	56±12	54±15
Triglycerides, mg/dL*	113±70	97±62	112±65	132±77
Blood glucose, mg/dL*	97±12	95±10	97±12	101±13
Apo-B, mg/dL†	95±22	91±22	100±22	98±23
Apo-A1, mg/dL†	157±32	160±31	159±35	152±31

Continuous variables are expressed as mean±standard deviation. LDL-C: Cholesterol carried by low density lipoproteins. HDL-C; Cholesterol carried by high density lipoproteins. Apo-B: Apolipoprotein B; Apo-A1; Apolipoprotein A1. p value in the initial analysis among the three risk subgroups: * <0.001; †<0.01; ‡<0.05.

(p<0.05). A similar, though not significant trend was seen in the low risk subgroup, where the prevalence of plaque was 18% (95% CI 11-30) in patients with 2 or more risk factors and 10% (95% CI 6-15) in patients with 0 to1 risk factors (p=0.08). In the high risk subgroup the differences were not significant (Figure 2)

DISCUSSION

The cardiovascular risk stratification proposed by the new American guidelines is based on an equation developed in a combined cohort of United States patients without atherosclerotic disease with a very easily accessible set of variables in primary care including (age, gender, race, total cholesterol, HDL-C, systolic blood pressure, antihypertensive treatment and smoking). The approach of these guidelines differs from the current recommendations of SAC and the National Ministry of Health which, with SAC's support, has adopted the use of the World Health Organization risk prediction charts for American coun-

tries in the B region. (5)

This new stratification proposal prompted our interest in assessing the applicability of the method in our population. For this purpose, the equation was used in a cohort of consecutive primary prevention patients treated at our institution and we found that just over a third (37%) of this population was stratified as absolute high risk (score≥7.5%). This high percentage coincides with a multicenter study performed in six cardiology centers in the Autonomous City of Buenos Aires and Greater Buenos Aires, where the application of the new guidelines' score showed that 33% of this population was also stratified as high risk and therefore with absolute indication for statin therapy according to the new guidelines. (9) Interestingly, almost an additional 18% of our population of patients was classified as intermediate risk (score≥5 and<7.5%) with potential statin indication.

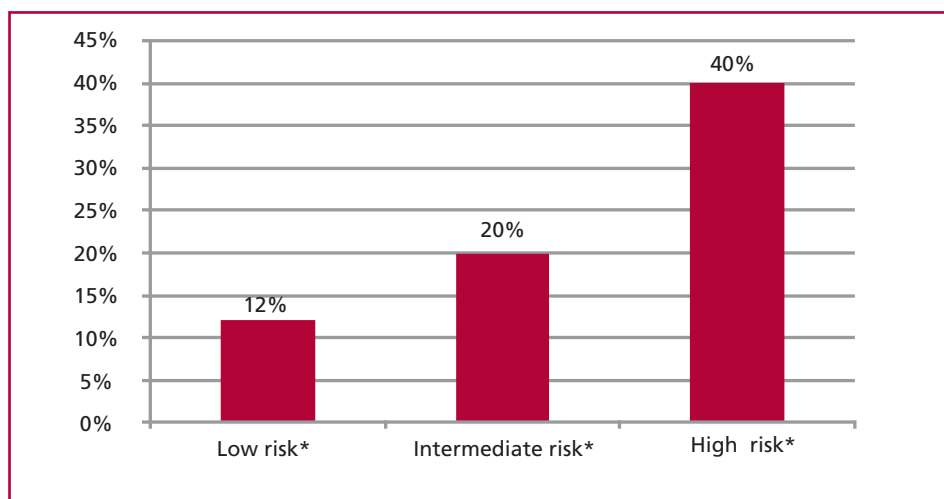Algorithms and equations are useful to establish population risk but their effectiveness to predict in-

Fig. 1. Prevalence of subclinical atherosclerosis according to the 2013 ACC-AHA risk groups. *p <0.001
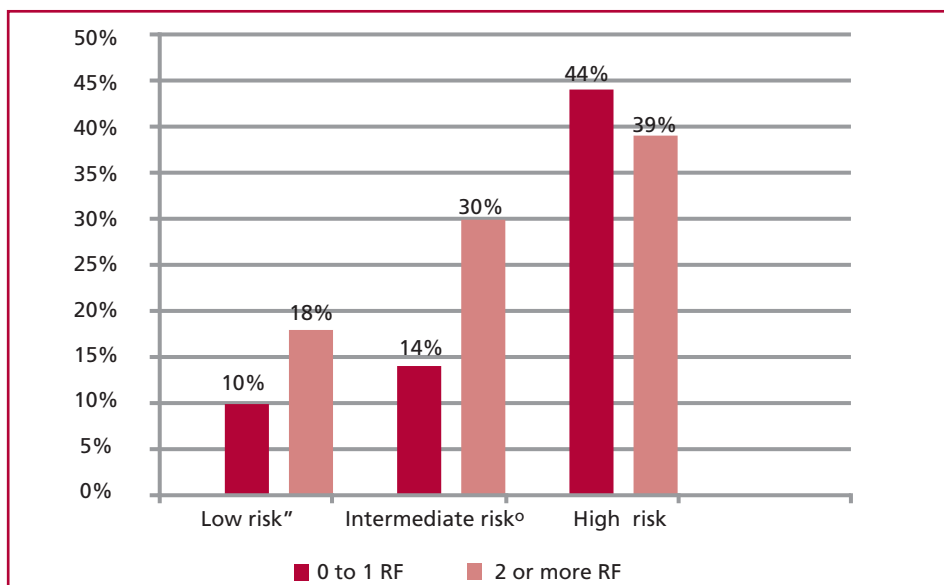

Fig. 2. Prevalence of subclinical atherosclerosis based on subgroups according to the number of risk factors. "p=0.08; °p<0.05

dividual risk may vary since there is a sum of factors and time and degree of exposure to these factors involved in atherosclerosis. (10) Therefore early detection of SCA may be useful in identifying subgroups at higher risk.

The new risk stratification guidelines (11) do not recommend the use of carotid echocardiography. This recommendation is based on the meta-analysis by Den Ruijter et al., (12) which included 14 population studies analyzing IMT in risk prediction. In this meta-analysis IMT evaluation did not add clinical significance to the classic Framingham score. (12) However, the study did not consider plaque assessment, which has been shown to be a better risk predictor compared with IMT in several prospective studies. (4, 13-17) Additionally, more recent studies have found that plaque characteristics, total plaque area and number of plaques and segments may have additional predictive value. (16, 17)

Initial studies in our country using carotid and femoral echocardiography show a high prevalence of SCA, which is particularly higher in subgroups at increased cardiovascular risk. (18) The overall prevalence of SCA in our population, verified by plaque in carotid echocardiography, was 25% with a significantly higher prevalence in high-risk patients compared to the low or intermediate risk group according to the new American guidelines. These findings are consistent, but are in the lower range of those reported by two other recent studies where, with local population and similar methodology, the overall prevalence of SCA ranged from 28% to 33%. (9, 19) These studies also found that the prevalence of plaque increased significantly according to risk in different subgroups using different strategies and scores for cardiovascular risk stratification. (9, 19) The differences observed with other publications are probably due to the fact that our population had a lower risk than that involved in other investigations. The population included in this study was characterized by a lower prevalence of smoking and lower levels of total cholesterol, LDL-C and triglycerides and higher levels of HDL-C. All these factors can influence the prevalence of plaque and might explain the disparities among the different studies mentioned.

Additionally, we also observed differences in the levels of hs-CRP and the proportion of patients with inflammatory response among the different risk groups stratified according to the new American guidelines, which seems to confirm in our population findings in the NAHANES cohort of patients, where high levels of hs-CRP were mainly attributable to the combination of classical risk factors. (20) In our population, just over half of the patients were at high or intermediate risk (stratified according to the new guidelines) associated to a high prevalence of carotid plaque and increased inflammatory activity.

Although traditional risk factors are components of different risk equations, their absolute number in each subject may provide additional information on individual risk stratification. This concept has been supported by several cohorts of patients showing the predictive significance of standard risk factors added to the risk prediction of cardiovascular atherosclerotic events. In those patients adding more than one risk factor, long-term probability of cardiovascular events is higher. (21, 22) In the present study, when subjects at intermediate risk, defined by ACC/AHA guidelines, were sub-stratified according to the number of risk factors, it was seen that those who had 2 or more risk factors had a significantly higher prevalence of SCA. A similar though not significant trend was observed in the subgroup of patients at low risk, while no differences were observed in patients stratified at absolute high risk.

Some useful implications for clinical practice arise from these findings. In our primary prevention population, 55% of subjects were ranked as high or intermediate risk and therefore would have absolute or potential indication of statins according to the American guidelines' recommendations. This increase in the potential use of statins has been described based on studies of both the American and our country's population, mainly at the expense of a greater indication in male, hypertensive patients, aged 60-75 years. (9, 23) These three variables (age, male gender and hypertension) significantly differentiated the three populations at risk in our study.

Additionally, in 18% and 30% of patients with low and intermediate risk, respectively, with 2 or more risk factors, we have detected evidence of SCA. These findings may be useful to select individuals in whom carotid echocardiography should be performed as part of the individual cardiovascular risk assessment, as an additional element to decide on a therapeutic approach, considering that imaging studies performed to all patients in primary prevention would increase the cost of risk stratification, with a negative impact on the health system. These findings should be confirmed by future prospective investigations aimed at evaluating cost-effectiveness of non-invasive studies in risk stratification and the degree of applicability of the ACC/AHA score in our population.

Limitations

The current ACC/AHA guidelines are not validated for our population and, therefore, the conclusions of their use in our country should be treated with caution. Our study is observational, based on the inclusion of consecutive patients in a prevention database and part of the clinical data come from a retrospective review of patients' charts and medical history, entailing potential limitations regarding accuracy and internal validity of some of the clinical variables collected in relation to prospective designs.

CONCLUSIONS

Application of the current ACC/AHA guidelines in our

population of primary prevention patients suggests that half of them should have potential or absolute indication of statins. Evaluation of SCA added to the presence of 2 or more risk factors in low or intermediate risk patients identifies a subgroup of patients with different risks, beyond the stratification of the new American guidelines, which could be useful in the decision making of the individual therapeutic management of these patients.

Conflicts of interest

None declared. (See authors' conflicts of interest forms in the website/Supplementary material).

Acknowledgements

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