

# Usefulness of the Presence and Type of Carotid Plaque to Predict Cardiovascular Events in High-Risk Patients

CARLOS A. INGINO<sup>MTSAC</sup>, MARTA L. KURA, ROGELIO A. MACHADO<sup>MTSAC</sup>, JUAN M. PULIDO, M. MARCELA ARCHER, ALEJANDRO CHERRO<sup>MTSAC</sup>, JOSÉ F. VILA, GASTÓN A. RODRÍGUEZ GRANILLO, PEDRO LYLYK

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## Address for reprints:

Dr. Carlos A. Ingino  
Libertador 6647  
(1428) Ciudad Autónoma de  
Buenos Aires  
Phone (011) 4014-7000  
e-mail: cingino@lylyk.com.ar

## SUMMARY

### Background

Carotid atheromatosis is an early manifestation of subclinical atherosclerosis that can be determined in a rapid, economic, repeatable and non-invasive fashion. The anatomic correlation and its association with risk factors and different manifestations of advanced atherosclerosis have been clearly demonstrated. The determination of the intima-media thickness and the presence and type of plaques in the carotid bulb are used to assess carotid atheromatosis in patients with risk factors and to evaluate response to treatment, as this method has an independent predictive value for ischemic coronary and cerebrovascular ischemic events.

### Objective

To determine whether the presence and type of carotid plaques (CPs) add any information to predict future cardiovascular events in high-risk patients.

### Material and Methods

A total of 502 high-risk patients (with multiple risk factors or history of vascular event) underwent ultrasound evaluation of maximum intima-media thickness (IMT<sub>max</sub>), presence (localized protrusion of the vessel wall) and type of (fibrocalcific plaque or fibrolipid plaque) CP, flow mediated dilation of the brachial artery (FMD, brachial artery diameter recorded at baseline and after 5 minutes of brachial ischemia). The following variables were considered abnormal: presence and type of CP, IMT<sub>max</sub> >1.1 and FMD <5%. Endpoints included vascular events or mortality. Markers of vascular disease and traditional risk factors (RFs) (age, diabetes, hypertension, dyslipemia, smoking habits and components of the metabolic syndrome) were analyzed together using Cox proportional-hazards regression model and Kaplan-Meier curves.

### Results

Mean age was 65.5±8.8 years and 354 were men; 43 events occurred during an average follow-up of 21 months. The presence of CP (RR 5.6; p <0.001), dyslipemia (RR 5.5; p <0.005), IMT<sub>max</sub> (RR 3.2; p <0.005), age > 65 years (RR 2.7; p <0.003), systolic hypertension (RR 2.5; p <0.025), HDL-C <50 mg/dl (RR 2.4; p <0.01), metabolic syndrome (RR 2.2; p <0.02), and triglyceride levels >130 mg/dl (RR 2.1; p <0.02) were predictors of events. After adjusting for RFs, CP was the most powerful predictor (RR 3.13; p <0.05). The incidence of events was 2.3% in the absence of CP, 8.8% with fibrolipid plaque, and 13.4% with fibrocalcific plaque p <0.001).

### Conclusions

The presence and type of CP and IMT<sub>max</sub> are markers of early vascular disease providing prognostic information independent of RFs. FMD did not provide additional information in this group. This simple, non-invasive method may be clinically useful in the evaluation of the risk of vascular events.

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## Key words

> Endothelium - Atherosclerosis - Risk Factors - Prognosis

**Abbreviations >**

<b>TIA</b>	Transient ischemic attack	<b>HT</b>	Hypertension
<b>HDL-C</b>	High density lipoprotein-cholesterol	<b>MI</b>	Myocardial infarction
<b>LDL-C</b>	Low density lipoprotein-cholesterol	<b>CP</b>	Carotid plaque
<b>DLP</b>	Dyslipemia	<b>BAR</b>	Brachial artery reactivity
<b>DM</b>	Diabetes mellitus	<b>SL</b>	Sedentary life
<b>RF</b>	Risk factor	<b>MS</b>	Metabolic syndrome
<b>IMT</b>	Intima-media thickness	<b>SH</b>	Smoking habits
<b>IMTmax</b>	Maximum intima-media thickness	<b>TG</b>	Triglycerides

**BACKGROUND**

Carotid atheromatosis is an early manifestation of subclinical atherosclerosis that may be determined in a rapid, inexpensive, repeatable and non-invasive fashion using B-mode Doppler ultrasound of the extracranial carotid arteries. The anatomic correlation (1) and its association with risk factors (2-13) and different manifestations of advanced atherosclerosis (2-5, 7, 10, 12, 13) has been clearly demonstrated. Nowadays, the determination of the intima-media thickness (IMT) and the presence and type of plaques in the carotid bulb are used to assess carotid atheromatosis in patients with risk factors (RFs) and to evaluate response to treatment, as this method has an independent predictive value for ischemic coronary and cerebrovascular events. (2-13)

The endothelium is a key regulator of vascular homeostasis that may modify the vascular phenotype. (14) The functional abnormalities of the endothelium precede the development of atherosclerotic changes and contribute to the progression of the disease and the presentation of the acute event. (15) Different techniques - initially invasive - were used to evaluate the aspects of endothelial function and for the early identification of the risk of developing vascular events. (16 - 18) As endothelial dysfunction is a systemic anomaly, Celermeyer (19) developed a method based on non-invasive ultrasound of the brachial artery after the production of forearm transient ischemia. This technique is based on the principle that because of shear forces due to flow increase in the brachial artery, endothelial cells are activated and nitric oxide is released leading to vasodilation of the artery.

The goal of this investigation was to analyze the predictive value for developing cardiovascular events of determining maximum intima-media thickness (IMTmax), the presence and type of carotid plaque (CP) and brachial artery reactivity (BAR) test by flow mediated dilation of the brachial artery (FMD) in patients at high-risk for cardiovascular disease.

**MATERIAL AND METHODS**

Between August 2003 and August 2008, a total of 502 consecutive patients were included, constituting a retrospective cohort. The information was retrieved from the clinical records of high-risk patients referred for vascular evaluation (carotid artery ultrasound imaging and non-invasive assessment of flow-mediated dilation). We included subjects with a history of a cardiovascular event or with two RFs or greater (hypertension, dyslipemia, diabetes and/or smoking habits), who allowed us to use their medical data for this study. The study protocol was presented to and approved by the Committee on Ethics of the participant institutions.

The development of events during follow-up was verified at medical visits (68%) or by phone calls following a pre-specified questionnaire (32%). In both cases, the

investigators were blinded to the results of the non-invasive studies related with the present investigation.

In all patients, IMTmax, the presence and type of CP and BAR were evaluated following a previous protocol. (13)

**Measurement of intima-media thickness**

All the studies were performed using an ultrasound tomography system Philips HD11XP and a 12 MHz linear transducer. The IMT was measured in the posterior wall of both common carotid arteries, 2 mm proximally from the carotid bulb (Figure 1). The images were captured using specially designed semi-automated software (M<sup>2</sup>Ath method Std<sup>®</sup>). The software measured the IMT on a 10-mm segment of the vessel considering between 100 and 200 measurement points (10-20 cm). We took as valid the determination that was above 70% of all measurements (QI 0.90 in the automatic window, Figure 1 A). Mean and maximum IMT were determined in each carotid artery; we used an upper limit of 1.1 mm of IMTmax based on the results of a previous study by our group. (13)

**Common carotid arteries, carotid bulbs and internal carotid arteries**

The common carotid arteries, the extracranial internal carotid arteries and the carotid bulbs were bilaterally explored with B-mode ultrasound to detect the presence of CPs. A plaque was defined as an irregular protrusion of a segment from the linear surface of the intima-media layer of the vessel (Figure 1 B and C). The type of plaque was categorized as:

- A. Fibrolipid plaque: low echogenicity, similar to that of blood and/or soft tissues (Figure 1 B).
- B. Fibrocalcic plaque: high echogenicity, similar to that of bones (Figure 1 C).

**Brachial artery reactivity test**

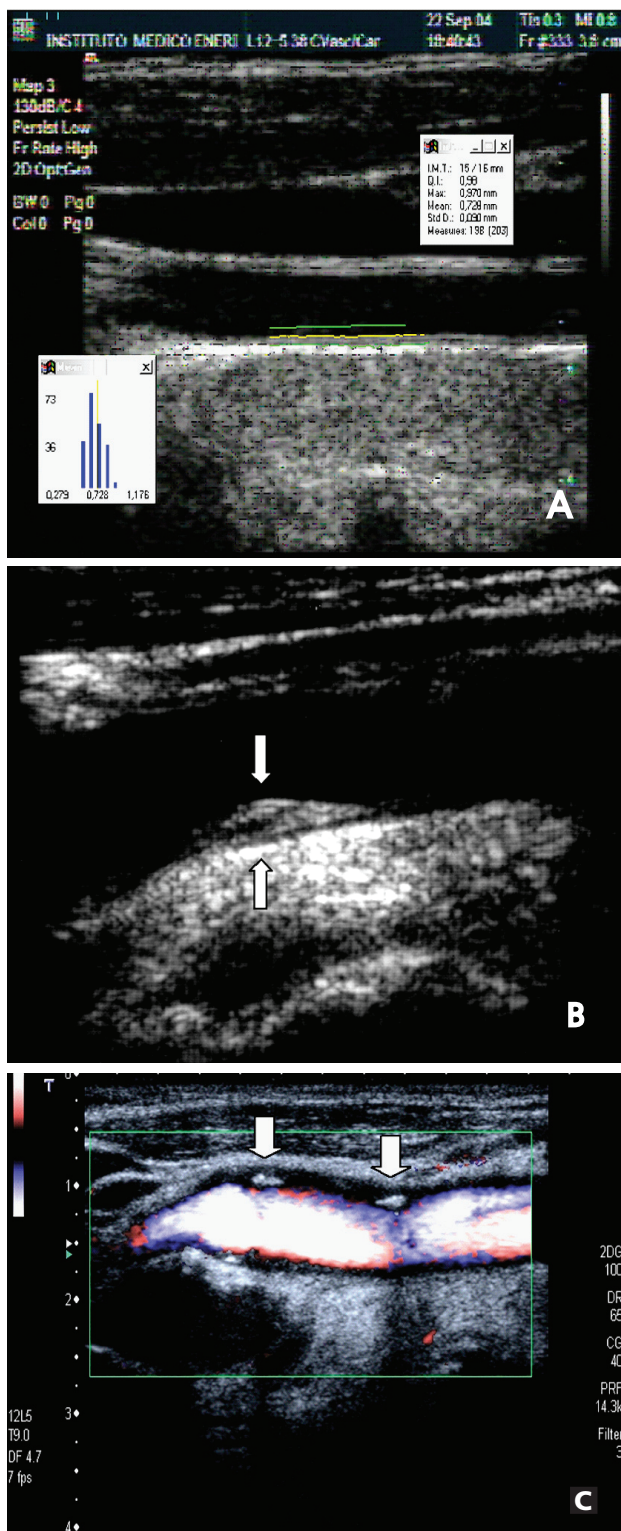
All the patients underwent BAR test taking their habitual medication after being informed about the characteristics of the exam. Studies were conducted after a fast of 4 hours with the subjects supine and after 5 minutes of rest, at temperature controlled environment between 24°C and 25°C according to a previously published protocol. (13)

The subject's right arm was comfortably immobilized in the extending position, allowing for ultrasound scanning of the brachial artery 2 - 4 cm above the antecubital fossa in the longitudinal section; gain and depth settings were optimized. The brachial artery diameter, mean velocities and blood flows were measured at rest and during the diastole. Thereafter, arterial occlusion was created by cuff inflation to 240 mm Hg for 5 minutes; the determinations were repeated one minute after cuff release. The percent change in brachial arterial diameter was determined (BAR).

**Clinical definitions**

1. Hypertension (HT): average of two blood pressure determinations of systolic pressure of 140 mm Hg or

greater and diastolic pressure of 90 mm Hg or greater after a 5-minute rest period, or prescription of antihypertensive drugs..



**Fig. 1.** A. Semi-automated measurement of carotid intima-media thickness using software M'Ath Std. B. Fibrolipid plaque (arrows) in the right common carotid artery proximally to the carotid bulb. C. Two fibrocalcic plaques (arrows) in the left common carotid artery.

- Smoking habits (SH): regular daily consumption of 10 cigarettes in the last 12 months.
- Dyslipemia (DLP): total cholesterol > 200 mg/dl; or triglycerides > 150 mg/dl; or HDL-cholesterol < 50 mg/dl in women or < 40 mg/dl in men; or indication of lipid lowering agents.
- Diabetes (DM): fasting glycemia > 125 mg/dl in two determinations, or incidental finding of glycemia > 200 mg/dl, or indication of hypoglycemic drugs.
- Metabolic syndrome (SM): defined by the presence of three or more criteria of the modified National Cholesterol Education Program Adult Treatment Panel III (20): waist circumference (men  $\geq 102$  cm and women  $\geq 88$  cm), systolic blood pressure  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 85$  mm Hg, or on antihypertensive drug treatment in a patient with a history of hypertension, fasting glucose  $\geq 100$  mg/dl or on drug treatment for elevated glucose, triglycerides  $\geq 150$  mg/dl or on drug treatment for elevated triglycerides, HDL cholesterol < 40 mg/dl in men or < 50 mg/dl in women.
- History of vascular disease: hospitalization due to myocardial infarction (MI) or stroke, old MI or stroke, history of myocardial revascularization surgery or percutaneous coronary intervention, angina with documented ischemia or documented transient ischemic attack (TIA), intermittent claudication or abdominal aorta aneurysm, significant lower extremity arteries disease documented by Doppler ultrasound.
- Cardiovascular event during follow-up: development of angina with documented ischemia, TIA, intermittent claudication, myocardial infarction or stroke, mortality due to cardiovascular event.
- Sedentary life (SL): regular physical activity < 60 min/week in a subject without job or < 45 min/week in an active subject.

#### Statistical Analysis

Qualitative variables were expressed as absolute values, proportions and/or percentages. Continuous variables were expressed as means and standard deviations and normal distribution was assessed using the goodness of fit test (K-S). The chi square test was used to compare discrete variables and continuous variables were analyzed using the Student's *t* test assuming normal distribution and equal variances.

The development of events in the different risk groups (without carotid plaque, with fibrolipid plaque and fibrocalcic plaque and between groups with different risk factors) was evaluated using the Kaplan-Meier method; survival curves were compared using the log-rank test. The multivariate analysis was performed using the Cox proportional-hazards regression model. The risks were expressed as relative risk (RR).

The apparent increase in cardiovascular events was corroborated using the chi-square test for trend. (21) Statistical analysis was performed using SPSS 13.0 statistical package. A two-tailed *p* value = 0.05 was considered statistically significant.

#### RESULTS

A total of 502 patients ( $65.5 \pm 8.8$  years, 352 were men) with a history of previous vascular events or 2 two risk factors or greater were included. The characteristics of the study population are described in Table 1. Table 2 shows the data obtained by Doppler ultrasound.

During an average period of 21 months (range, 2



to 60), 43 events occurred. The univariate analysis of cardiovascular risk estimators is shown in Table 3. The presence of CP (RR 5.6;  $p < 0.001$ ), DLP (RR 5.5;  $p < 0.005$ ), IMT (RR 3.2;  $p < 0.005$ ), age  $> 65$  years (RR 2.7;  $p < 0.003$ ), HDL-C  $< 50$  mg/dl (RR 2.4;  $p < 0.01$ ), systolic HT (RR 2.5;  $p < 0.025$ ), metabolic syndrome (RR 2.2;  $p < 0.02$ ), and TG levels  $> 130$  mg/dl (RR 2.1;  $p < 0.02$ ) were the strongest predictors of events. Diabetes and BAR were not predictors of events in this group of patients.

When the different predictors were added to the Cox model, CP and IMT on the one hand, and DLP, low HDL-C and high TG levels on the other hand gave additional information and resulted independent predictors of events (Table 3). This independence persisted after correcting for age (which was also

an independent predictor). Table 3 A shows the coefficients and the RR of the pooled logistic regression of the most efficient variables; subjects with CP, DLP and age  $> 65$  years have a  $RR = 3.45 \times 3.87 \times 2.05 = 27.4$ , representing a risk 27 times greater compared to that of subjects without any of these three factors (Table 3 B). Interestingly, IMT loses significance when the variable CP is in the model; the same occurs with HDL-C and TG in the presence of DLP.

Figure 2 illustrates the Kaplan-Meier curves of survival free of events associated with the presence CP and DLP (one factor, two factors or absence of factors).

The incidence of events was greater in patients with fibrocalcic plaque ( $n = 217$ , 13.4%) compared to fibrolipid plaque ( $n = 114$ , 8.8%) and absence of CP ( $n = 171$ , 2.3%) ( $p < 0.001$ , chi square for trend). This trend can also be seen in the survival curves for each class of subjects (Figure 3).

**Table 1.** Characteristics of the population

	Value	SD
Age, years	65.5	8.8
Men, %	70.5	
BMI	27.5	4
Abdomen, %	43.2	
Sedentary life, %	72	
Smoking habits, %	12	
Dyslipemia, %	72.3	
Diabetes, %	17.3	
Hypertension, %	73.5	
Previous event, %	35.9	
Metabolic syndrome, %	36.7	
Glycemia, mg/dl	102.8	19.8
Total cholesterol, mg/dl	214.8	34.3
HDL-cholesterol, mg/dl	52.6	13.6
LDL-cholesterol, mg/dl	132.3	31.3
Triglycerides, mg/dl	130.9	56.6
Diastolic blood pressure, mm Hg	83.6	7.8
Systolic blood pressure, mm Hg	145.1	13.2

Abdomen: indicates waist circumference above the superior limit.

**Table 1.** Events during follow-up.

Events	n (%)
AMI - Angina with ischemia - Myocardial revascularization	17 (39.5)
Stroke - Transient ischemic attack - Carotid artery stenting - Vertebral artery stenting	18 (41.9)
Peripheral vascular disease - Abdominal aorta aneurysm	6 (13.9)
Cardiovascular mortality	2 (4.7)
Total	43 (100)

## DISCUSSION

Our investigation corresponds to a cohort study based on retrospective data of 502 patients with high cardiovascular risk. The presence of CP, especially fibrocalcic plaque, was an independent predictor of vascular events.

Multivariate Cox regression analysis of the pooled data of ultrasound, clinical and laboratory variables demonstrated that, on the one hand, both types contribute with independent information about the prognosis while, on the other hand, the simultaneous inclusion of the same type of variables produces the loss of significance of few of them. For example, when plaque and IMT were included together, the latter lost statistical significance, suggesting that the information had been provided by the former. The components of DLP also lost significance when they were included with DLP. In this way, we observe that the same type of variables share information and tend to neutralize each other, while ultrasound and humoral variables add prognostic information. Finally, the statistical significance of age remained in the presence of anatomical and humoral variables,

**Table 1.** Results of Doppler ultrasound in the study population

	Value	SD
Average right IMT, mm	0.87	0.21
Average left IMT, mm	1.01	0.23
Right IMTmax, mm	0.93	0.23
Left IMTmax, mm	1.17	0.25
Plaque, %	65.9	
Fibrocalcic plaque, %	64.7	
Fibrolipid, %	44.2	
Brachial artery at rest, mm	4.81	0.74
Brachial artery one minute after 5-minute ischemia, mm	4.96	0.76

IMTmax: Maximum intima-media thickness.

**Table 3 A.** Cox proportional-hazards regression model for each of the predictor variables examined separately.

Variable	Coefficient	SE	z	p	Coefficient
Plaque	1.72544	0.52712	3.27	0.001	5.62 (2.00-15.78)
IMT	1.16501	0.37437	3.11	0.002	3.21 (1.54-6.68)
Age > 65 years	0.99671	0.33729	2.96	0.003	2.71 (1.40-5.25)
DLP	1.71151	0.59782	2.86	0.005	5.54 (1.72-17.87)
HDL-C < 50 mg/dl	0.88572	0.32794	2.70	0.007	2.42 (1.284-61)
TG > 130 mg/dl	0.76279	0.31380	2.43	0.015	2.14 (1.16-3.97)
Systolic HT	0.92409	0.41218	2.24	0.025	2.52 (1.12-5.65)
MS	0.77862	0.30739	2.53	0.010	2.18 (1.19-3.98)

**Table 3 B.** Pooled logistic regression of the most efficient variables

1. Variable	Coefficient	SE	z	p	Coefficient
Plaque	1.23840	0.54378	2.28	0.023	3.45 (1.19-10.00)
DLP	1.35225	0.60524	2.23	0.026	3.87 (1.18-12.66)
Age > 65 years	0.71797	0.34004	2.11	0.035	2.05 (1.05-3.99)

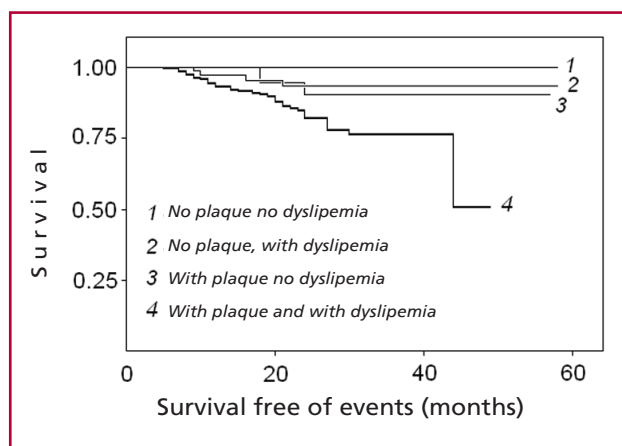
  

2. Variable	Coefficient	SE	z	p	Coefficient
Plaque	1.38745	0.53606	2.59	0.01	4.00 (1.40-11.45)
HDL-C < 50 mg/dl	0.88086	0.33572	2.62	0.01	2.41 (1.25-4.66)
Age > 65 years	0.89727	0.34259	2.62	0.01	2.45 (1.25-4.80)

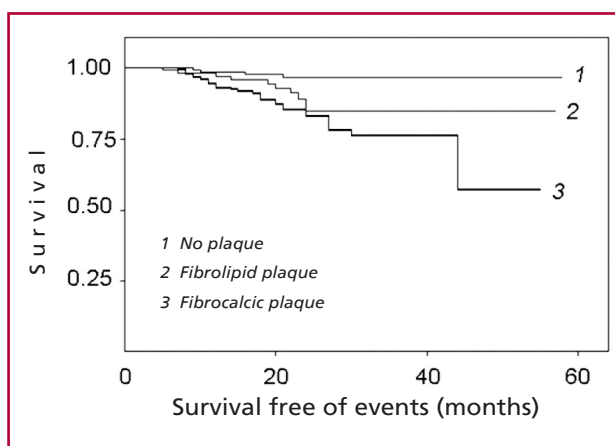
  

3. Variable	Coefficient	SE	z	p	Coefficient
IMT	1.02514	0.37672	2.72	0.01	2.79 (1.33-5.83)
DLP	1.60133	0.59800	2.68	0.01	4.96 (1.54-16.01)
Age > 65 years	0.84648	0.33701	2.51	0.01	2.33 (1.20-4.51)

SE: Standard error. RR: Relative risk; 95% confidence interval between brackets. IMT: Intima-media thickness. DLP: Dyslipemia. HDL-C: High density lipoprotein-cholesterol TG: Triglycerides. HT: Hypertension MS: Metabolic syndrome



**Fig. 2.** Kaplan-Meier curves of survival free of events associated with the presence CPs and DLP. 1 (no plaque and no DLP) vs. 2 (no plaque and with DLP); 1 vs. 3 (with plaque and no DLP) and 1 vs. 4 (with plaque and with DLP),  $p < 0,001$ ; 2 vs. 4 y 3 vs. 4,  $p < 0,05$ ; 2 vs. 3, ns.



**Fig. 3.** Kaplan-Meier curves of survival free of events associated with the type of plaque. 1 (no plaque) vs. 2 (fibrolipid plaque),  $p < 0.05$ ; 1 vs. 3 (fibrocalcic plaque),  $p < 0.001$ ; and 2 vs. 3, NS.

demonstrating that it adds independent prognostic information. In this way, the combination of predictors of events included one of each type of markers and age; the combinations plaque-DLP-age and plaque-

HDL-C-age were the strongest combined predictors.

The relative risks are multiplicative, (22) meaning that the global risk for each subject may be estimated by multiplying the corresponding RR for each abnormal

variable. In this was, as we have shown in the section Results, the RR for a subject with plaque-DLP-age > 65 years would be 27 times greater compared to that of a person without these factors. This means that the risk ratio will be considerable higher than then one obtained for each variable examined separately.

These results are consistent with those reported by other publications. The carotid and the coronary arteries are the most common sites of atherosclerotic compromise and share epidemiologic aspects. (23, 24) Initially, smooth muscle cell proliferation increases IMT in the carotid arteries; then macrophages migrate into the intima becoming foam cells; fibrolipid plaques develop and are subsequently calcified. (25) In coincidence with this evolution of carotid atherosclerotic disease, Kanadasi et al. (26) demonstrated that the presence of fibrocalcic CP was a better predictor of coronary artery disease compared to fibrolipid CP and to increased IMT. Grotta et al. showed a strong correlation between the extent and the severity of coronary artery disease and the progression of carotid atherosclerosis. (27)

Increased IMT is an early manifestation of atherosclerosis. It represents an adaptive change to wall stress and shear forces and is also associated with a greater risk of coronary and cerebrovascular events. (2-12)

Probably, both atherosclerotic processes, increased IMT and CP, correspond to different mechanisms and stages of the disease. IMT is associated with hypertrophy of the media layer, probably due to a genetic origin, (28, 29), while the development of CP represents a later stage related with inflammation, oxidation and endothelial dysfunction, as well as cellular proliferation and migration of smooth muscle cells. (30)

The bibliographic information about RFs deserves to be analyzed. Khot et al. (31) reported that 62% of patients with coronary artery disease presented between 0 and 1 of the conventional risk factors (HT, SH, hypercholesterolemia and DM); 19% lacked any of the RF and 43% had only 1. Therefore, coronary risk scores as the Framingham Risk Score may incorrectly identify as low risk patients those who will develop coronary artery disease. The guidelines for the treatment of hypercholesterolemia (ATP III) recognize this fact mentioning that major RFs may explain only some of the variability in coronary artery disease risk in the population of the United States. (32)

In our study, the incidence of major RFs in healthy controls was also high. The analysis by Greenland et al. included three prospective cohort studies: the Chicago Heart Association Detection Project in Industry, with a population sample of 35642 employees; screenees for the MRFIT, including 347 978 men; and a population-based sample of 3295 men and women from the Framingham Heart Study (FHS); follow-up lasted 21 to 30 years across the studies. This analysis

demonstrated prevalence > 90% of exposure to 1 or more major RFs before fatal and non-fatal MI, and the authors confirmed that "MI rarely occurs in the absence of a major RF". However, the prevalence of major RFs among controls was about 70%. (33) The results of the INTERHEART study were similar. (34) Nine RFs (SH, ApoB/ApoA1 ratio, HT, DM, abdominal obesity, psychosocial factors, lack of daily consumption of fruits and vegetables, regular alcohol consumption and SL) account for most of the risk of myocardial infarction in 90% of men and 93% of women. However, the prevalence of each RF in the populations with and without infarction indicated low sensitivity and specificity for each RF (SH 60% vs. 38%, ApoB/ApoA1 ratio 39% vs. 20%, HT 39% vs. 22%, DM 18% vs. 8%, abdominal obesity 46% vs. 36%, psychosocial factors 10% vs. 18%, diet 32% vs. 42%, alcohol 24% vs. 24.4% and SL 14% vs. 19%, respectively). The challenge remains about how to distinguish one group from the other. In many of these cases, a non-invasive approach for the evaluation of vascular disease might be helpful. Treatment of hypercholesterolemia is currently the mainstay to prevent coronary artery disease, and despite cholesterol level is a surrogate marker of vascular health status, its value to predict coronary events is limited. For example, in men with early coronary artery disease, only 35% presented high levels of LDL-cholesterol (35); similarly, a retrospective analysis of 222 young adults (25% were women) with myocardial infarction found relatively acceptable LDL-C and HDL-C levels (126 mg/dl and 43 mg/dl, respectively). (36) According to the NCEP guidelines, only 25% of male and 18% of female patients would have been identified as high-risk subjects and qualified for pharmacological treatment. The prevalence of atherosclerosis in subjects with no clinical or angiographic evidence of significant coronary disease was evaluated by Tuczku et al. using intravascular ultrasound. This study demonstrated that increased intima-media thickness was present in 1 of 6 teenagers and that the prevalence of coronary artery disease was 85% in subjects > 50 years old. (37) About 18% of subjects with coronary atherosclerotic plaque detected by multi-detector computed coronary angiography did not report any traditional RFs. (38) Risk-scoring methods based on models built from RFs are useful to predict cardiovascular events in a population, yet, the individual sensitivity and specificity of these scores is low. Similarly, age is an important predictor but is not useful to determine which patient has greater risk.

The Screening for Heart Attack Prevention and Education (SHAPE) Task Force report has recently proposed non-invasive cardiovascular screening in the at-risk population using computed tomography scanning and carotid Doppler ultrasound. (39) The SHAPE Guideline calls for noninvasive screening in asymptomatic intermediate-risk patients measuring coronary artery calcification by computed tomography

scanning and carotid artery intima-media thickness and plaque by ultrasonography. The screening results (severity of subclinical arterial disease) combined with risk factor assessment are used for risk stratification to initiate appropriate therapy

The present investigation suggests that a group of subjects at risk for cardiovascular events might benefit from an inexpensive, accessible and repeatable study as carotid ultrasonography. The results of the OSACA2 study confirm our findings: carotid IMT is an independent predictor of vascular events in high-risk patients in whom risk factors are managed clinically. (40)

However, a recent review about the value of IMT to predict cardiovascular risk (41) concluded that: (1) IMT was an independent but relatively modest predictor of coronary heart disease; (2) IMT was an independent predictor for stroke, slightly better than for coronary artery disease as judged by the relative risks of both events; (3) IMT added little to the coronary artery disease prediction by risk factors and (4) the CHD prediction by IMT was inferior to that by ultrasonography-assessed carotid plaque because plaque may be more representative of atherosclerosis than IMT. (42)

#### Study limitations

This study evaluated only high risk patients, thus, the results should not be extrapolated to the general population. These results have not been compared with risk scores as the Framingham Risk Score, or with the prognostic information provided by other non-invasive tests in similar patients.

#### CONCLUSIONS

The present investigation has demonstrated that anatomical markers of vascular disease can provide prognostic information for the follow-up of certain patients at high-risk of cardiovascular events, providing additional information to that supplied by the traditional risk factors.

#### RESUMEN

#### Diagnóstico y tratamiento quirúrgico del origen anómalo de las arterias coronarias

##### Introducción

La ateromatosis carotídea es una alteración temprana de la aterosclerosis subclínica que puede determinarse en forma rápida, económica, repetible y no invasiva. Su correlación anatómica y su asociación con los factores de riesgo y diferentes manifestaciones de aterosclerosis avanzada se han demostrado claramente. En la actualidad, la ateromatosis carotídea se utiliza con frecuencia creciente para caracterizar al paciente con factores de riesgo y para evaluar resultados terapéuticos mediante la determinación del grosor íntima-media carotídeo y de la presencia y el tipo de placas bulbares, ya que se ha demostrado su valor predictivo independiente para eventos isquémicos tanto coronarios como cerebrovasculares.

#### Objetivo

Determinar si la presencia y el tipo de placa carotídea (PC) agregan información para predecir futuros eventos cardiovasculares en pacientes de riesgo alto.

#### Material y métodos

Se estudiaron 502 pacientes de riesgo alto (múltiples factores de riesgo o antecedente de evento vascular) mediante la determinación del grosor íntima-media máximo (GIM<sub>máx</sub>), la presencia (elevación localizada) y el tipo de PC según apariencia ecográfica (fibrocálcica o fibrolipídica), la reactividad humeral dependiente del endotelio (RDE, valor basal arteria humeral vs. a los 5 min de isquemia braquial). Se consideró anormalidad la presencia y el tipo de PC, el GIM<sub>máx</sub> > 1,1 mm y la RDE < 5%. Los puntos finales incluyeron la ocurrencia de eventos vasculares o de muerte. Los marcadores de enfermedad vascular se analizaron junto con factores de riesgo (FR) clásicos (edad, diabetes, hipertensión, dislipidemia, tabaquismo y componentes del síndrome metabólico) por el método de riesgos proporcionales de Cox y curvas de Kaplan-Meier.

#### Resultados

Edad media 65,5 ± 8,8 años, 354 hombres, 43 eventos durante un seguimiento promedio de 21 meses. Fueron predictores de eventos la PC (RR 5,6; p < 0,001), la dislipidemia (RR 5,5; p < 0,005), el GIM<sub>máx</sub> (RR 3,2; p < 0,005), la edad > 65 años (RR 2,7; p < 0,003), la hiper-tensión sistólica (RR 2,5; p < 0,025), el C-HDL < 50 mg/dl (RR 2,4; p < 0,01), el síndrome metabólico (RR 2,2; p < 0,02), la trigliceridemia > 130 mg/dl (RR 2,1; p < 0,02). Ajustado por los FR, el predictor más potente resultó la PC (RR 3,13; p < 0,05). Los individuos sin PC presentaron un 2,3% de eventos, con PC fibrolipídica un 8,8% y con PC fibrocálcica un 13,4% (p < 0,001).

#### Conclusiones

Marcadores de enfermedad vascular temprana, como la presencia y el tipo de PC y el GIM<sub>máx</sub>, agregan información pronóstica independiente a los FR. La RDE no agregó información en este grupo. Una metodología simplificada de estudio no invasivo como la empleada puede ser de utilidad clínica en la evaluación del riesgo de eventos vasculares.

**Palabras clave** > Endotelio - Aterosclerosis - Factores de riesgo - Pronóstico

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