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CLINICAL INVESTIGATION

Carotid plaque is a predictor of major adverse cardiac and cerebrovascular events in patients undergoing coronary angiography

La presencia de placa carotídea es predictor de eventos adversos cardiacos y cerebrovasculares en sujetos sometidos a coronariografía

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Abstract

Introduction: *Carotid disease, measured as carotid intima-media thickness (CIMT) and carotid plaque (CP), is associated with major adverse cardiac and cerebrovascular events (MACCE) in people without the previous atherosclerotic disease; however, there are few published data in patients undergoing coronary angiography. The aim of the study is to determinate if the carotid disease is associated with MACCE after coronary angiography.* **Methods:** *A total of 390 consecutive patients underwent coronary angiography after exercise echocardiography and carotid ultrasonography between 2002 and 2013. MACCE was defined as stroke, myocardial infarction due to atherosclerosis progression or death due to a stroke or cardiac event.* **Results:** *Two patients were lost (0.5%). During a mean follow-up of 6.0 years (standard deviation of 2.9), 52 patients (13.4%) suffered MACCE. 1, 5, and 10 years, event-free survival was 96.4% (1.0), 88.7% (1.7), and 81.4% (2.8), respectively. Event rates at 10 years were higher in the CP group (23.2% vs. 10.2%, p = 0.013) and in the CIMT > 0.9 mm group (25.9% vs. 13.3%, p = 0.023). Multivariate analysis showed smoking habit (hazard ratio [HR] 2.51, 95% confidence interval [CI] 1.36-4.62, p = 0.003), glomerular filtration rate (HR 0.98, 95% CI 0.98-0.99), aortic stenosis (HR 2.99, 95% CI 1.24-7.21, p = 0.014), incomplete/no coronary revascularization (HR 1.97, 95% CI 1.06-3.67, p = 0.033), insulin treatment (HR 2.63, 95% CI 1.30-5.31, p = 0.006), and CP (HR 2.36, 95% CI 1.02-5.44, p = 0.044) as predictors of MACCE.* **Conclusions:** *CP is an independent predictor of MACCE in patients undergoing coronary angiography.*

Key words: *Carotid ultrasonography. Carotid plaque. Coronary artery disease. Major adverse cardiac and cerebrovascular events. Spain.*

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Resumen

La enfermedad carotídea, definida como grosor de íntima media (GIMC) y placa (PC), se asocia con eventos adversos cardiacos y cerebrovasculares (EACC) en sujetos sin aterosclerosis previa; sin embargo hay pocos datos en pacientes sometidos a coronariografía. El objetivo del estudio es determinar si la enfermedad carotídea se asocia a EACC en pacientes remitidos a coronariografía. **Métodos:** *Entre 2002 y 2013 390 pacientes fueron sometidos a coronariografía tras ecocardiograma de esfuerzo y ecografía carotídea. Se definió EACC como accidente cerebrovascular, infarto de miocardio por progresión aterosclerótica o muerte por accidente cerebrovascular o causa cardiaca.* **Resultados:** *Durante un seguimiento medio de 6 años (desviación estándar 2, 9) se registraron 2 pérdidas y 52 eventos (13,4%). La supervivencia media libre de eventos a uno, cinco y diez años fue 96.4% (1.0), 88.7% (1.7) y 81.4% (2.8). Hubo mayor número de eventos a 10 años en el grupo de PC (23.2% frente 10.2%, p = 0.013) y GIMC > 0.9 mm (25,9% frente 13.3%, p = 0.023). En el análisis multivariado los predictores de EACC fueron tabaquismo (hazard ratio [HR] 2.51, intervalo de confianza [IC] al 95% 1.36-4.62, p = 0.003), filtrado glomerular renal (HR 0.98 IC95% 0.98-0.99), estenosis aórtica (HR 2.99, IC 95% 1.24-7.21, p = 0.014), revascularización incompleta/no revascularización (HR 1.97, IC 95% 1.06-3.67, p = 0.033), tratamiento con insulina (HR 2.63, IC 95% 1.30-5.31, p = 0.006) y PC (HR 2.36, 95%CI 1.02-5.44, p = 0.044).* **Conclusiones:** *La PC es un predictor independiente de EACC en pacientes sometidos a coronariografía.*

Palabras clave: *Ecografía carotídea. Placa carotídea. Enfermedad arterial coronaria. Eventos adversos cardiacos y cerebrovasculares. España.*

Introduction

There is well-documented evidence for atherosclerosis as a systemic disorder[1-12]. Postmortem studies have shown a strong correlation between carotid and coronary artery disease (CAD)[1-3]. In the same line, carotid intima-media thickness (CIMT) and/or the presence of plaque carotid plaque (CP) have been identified as independent predictors of myocardial infarction (MI), stroke and death in asymptomatic and presumably healthy patients[4-12] improving the ability of risk functions to predict cardiovascular events[13].

Conversely to people without previous cardiovascular disease, there are few studies correlating carotid disease and new cardiovascular events in patients with ischemic heart disease, some of them showing contradictory results[14-20].

The aim of our study is to ascertain whether the carotid disease is a predictor of major adverse cardiac and cerebrovascular events (MACCE) in patients undergoing a coronary angiography regarding previous treadmill exercise stress echocardiography results.

Methods

Study population

This is a single-center retrospective study of patients submitted to coronary angiography after treadmill exercise stress echocardiography and carotid ultrasound were performed. From January 1, 2002, to December 31, 2013, 390 consecutive Caucasian patients older than 18 years with suspected CAD underwent coronary angiography in multiple projections using standard technique regarding exercise echocardiography results and physician's in charge of the patient criteria, mainly due to the persistence of symptoms. All patients signed an informed consent before testing. The study was approved by the Regional Ethics Committee.

Demographic, clinical, rest and exercise echocardiography, carotid, angiography, and treatment data were collected. Prior CAD was defined as previous MI[21], coronary revascularization, or angiographic documentation of any coronary stenosis ≥50%. Prior vascular disease was defined as prior CAD, stroke, transient ischemic attack or peripheral artery disease.

Rest and treadmill exercise stress echocardiography

Rest and exercise echocardiography was carried out according to the current European and American guidelines at the time of their performance[22-24].

Carotid ultrasonography

Carotid scans were performed immediately after stress test with the same exercise echocardiography ultrasound equipment using a high-resolution, non-harmonic B-mode ultrasound system (Philips Sonos 5500 between 2002 and 2005 and Philips iE33 after 2005; Philips Medical Systems) with a linear array (3-11 MHz) transducer. CP was defined as a focal structure encroaching into the

arterial lumen by > 0.5 mm, a distinct area of CIMT > 50% than the adjacent wall or CIMT > 1.5 mm[25-28]. CIMT was assessed as stated by the atherosclerosis risk in communities study[6] and current guidelines[25-28] using a semiautomated edge detection algorithm (Qlab; Philips 110 Medical Systems, Andover, MA, USA).

CIMT age- and sex-specific percentile values were defined according to previously published data in our country[29].

Carotid ultrasonography stored images were retrospectively analyzed by two imaging expert cardiologists blinded to MACCE. In case of disagreement, a third expert was consulted.

Coronary angiography

The significant angiographic disease was defined as stenosis ≥ 50% by visual assessment in any major epicardial arteries or their branches. CAD treatment was recorded as medical, balloon percutaneous coronary intervention (PCI), bare metal and drug-eluting stent PCI or coronary artery bypass grafting (CABG). Complete revascularization was defined as the treatment of any significant CAD in vessels ≥ 1.5 mm as estimated on the diagnostic angiogram during the local Heart Team conference.

Follow-up and end point

Follow-up data were obtained from the hospital database, medical records, and death certificates. In case of doubt, the Regional Mortality Registry was consulted. MACCE was defined as MI due to atherosclerosis progression, stroke and death due to MI, stroke, life-threating arrhythmias, cardiac arrest or unexpected and otherwise-unexplained sudden death. MI was defined as specified by the third universal definition of MI expert consensus document[21]. Patients with MI due to in-stent restenosis or thrombosis were censored at the time of the event. Stroke was defined as a loss of neurological function caused by an ischemic event, lasting for >24 h or leaving residual signs.

Statistical analysis

Categorical variables were reported as percentages and continuous variables as mean (standard deviation) when they are normally distributed or median (interquartile range) when their distribution departed from normal.

Cumulative events curves were calculated by Kaplan–Meier method and compared by log rank test.

Table 1. Clinical and biochemical baseline characteristics of enrolled patients

Variable	All patients n=390 (%)
Age (years)	66.0 (10.5)
Male sex (%)	296 (75.9)
BMI (Kg/m^2)	28.4 (3.9)
Hypertension	239 (61.3)
Hypercholesterolemia	245 (62.8)
Diabetes mellitus	131 (33.6)
Smoking habit	191 (49.0)
Family history of premature CAD	44 (11.3)
Obesity (BMI ≥ 30 Kg/m^2)	116 (29.7)
Atrial fibrillation	37 (9.5)
Prior CAD	205 (52.6)
Prior vascular disease	234 (60.0)
Chest pain	341 (87.4)
Fasting plasma glucose (mg/dL)	114.1 (33.0)
GFR (ml/min/1.73 m^2)	77.0 (24.1)
Total Cholesterol (mg/dL)	175.9 (44.5)
Low-density lipoprotein (mg/dL)	104.7 (36.2)
High-density lipoprotein (mg/dL)	41.6 (11.0)
Triglycerides	152.9 (106.9)

BMI: body mass index, CAD: coronary artery disease, GFR: glomerular filtration rate.

Cox's proportional hazards models were performed for univariate and multivariate analysis of the endpoint. In multivariate analysis, backward stepwise selection was used with an entry set at 0.2 significance level and a retention set of 0.1. $p < 0.05$ was considered statistically significant.

The statistical analysis was carried out with IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY).

Results

Of all patients, 2 (0.5%) were lost during follow-up. Baseline characteristics of subjects are summarized in tables 1 and 2.

Outcomes

During a mean follow up of 6.0 (2.9) years, 60 patients deceased (15.5%). The causes of death were

Table 2. Echocardiographic, carotid and angiographic baseline characteristics and medical treatment at discharge

Variable	All patients n=390 (%)
Left ventricular ejection fraction (%)	60.4 (8.49)
Left ventricular ejection fraction < 50%	42 (10.8)
Mitral valve regurgitation	239 (61.3)
Aortic valve stenosis	20 (5.1)
Aortic valve regurgitation	131 (33.6)
Positive stress echocardiography	283 (72.6)
Metabolic equivalents	7.46 (2.8)
Mean CIMT (mm)	0.88 (0.21)
CIMT > 0.9mm	171 (43.8)
Mean CIMT percentile ≥ 75th	236 (60.5)
CP	273 (70.0)
CAD ≥ 50%	295 (75.6)
1 vessel	115 (29.5)
2 vessels	89 (22.8)
3 vessels	91 (23.4)
PCI	165 (42.3)
CABG	31 (10.5)
Incomplete/no revascularization	191 (49.0)
Beta-blockers	315 (80.8)
Calcium channel blockers	89 (22.8)
Nitrates	132 (33.8)
Statins	349 (89.5)
Ezetimibe	22 (5.6)
Antidiabetic drugs	79 (20.3)
Insulin	35 (9)
Antiplatelet drugs	351 (90.0)
Oral anticoagulants drugs	29 (7.4)

CABG: coronary artery bypass grafting, CAD: coronary artery disease, CIMT: carotid intima-media thickness, CP: carotid plaque, PCI: percutaneous coronary intervention

non-cardiovascular events (fundamentally neoplasms) in 28 patients (46.7%), sudden death in 17 subjects (28.3%), MI in 5 patients (8.3%), heart failure in 5 patients (8.3%), arrhythmia in 3 patients (5%), and stroke in 2 patients (3.3%). MI was diagnosed in 42 patients (10.8%), 16 of them related to in-stent restenosis or thrombosis, and 12 patients suffered stroke (3.1%).

In the subgroup of 67 patients without significant CAD and previous vascular disease 29 subjects (43.28%) had CP in carotid ultrasonography. Neither AMI nor deaths were observed, just one stroke was reported in the subgroup of patients with CP.

MACCE was recorded in 52 subjects (13.4%). Mean annual event rate was 2.1%. Kaplan–Meier event-free survival was 96.4% (1.0) at 1 year, 88.72% (1.7) at 5 years, and 81.35% (2.8) at 10 years.

MACCE was higher in CIMT > 0.9 mm group with a mean annual event rate of 1.7% in the CIMT ≤ 0.9 mm compared to 2.7% in the CIMT > 0.9 mm group. Cumulative incidence of MACCE was 1.9%, 7.8%, and 13.3% versus 5.9%, 15.8, and 25.9% (p = 0.023) at 1, 5, and 10 years, respectively. CP presence was also predictor of MACCE with a mean annual event rate of 0.8% and cumulative incidence of 2.6%, 7.1 and 10.2% at 1, 5, and 10 years in the CP absence group and a mean annual event rate of 2.8% and cumulative incidence of MACCE at 1, 5, and 10 years of 4.1%, 13.2%, and 23.2% in the CP presence group (p = 0.013). Fig. 1 represents cumulative incidence of MACCE depending on carotid ultrasound characteristics.

Predictors of outcome

Univariate analysis showed age (Hazard Ratio [HR] 1.03, p = 0.040), diabetes mellitus (HR = 2.32, p = 0.002), smoking habit (HR = 1.87, p = 0.030), glomerular filtration rate (GFR) (HR = 0.98, p = 0.002), baseline left ventricular ejection fraction (HR = 0.96, p = 0.040), presence of aortic stenosis (HR 3.29, p = 0.007), metabolic equivalents in stress test (HR = 0.90, p = 0,046), CP (HR = 2.41, p = 0.017), CIMT > 0.9 mm (HR= 1.87, p = 0.025), number of coronary arteries affected (HR = 1.43, p = 0.006), incomplete revascularization (HR = 2.62, p = 0.001), and nitrates and insulin treatment (HR = 1.73, p = 0.049 and HR = 2.97, p = 0.001 respectively). Multivariate analysis of combined end point is represented in table 3.

Discussion

The present study shows that CP is an independent predictor of MACCE in patients undergoing coronary angiography.

Held et al. failed to demonstrate a significant association between CIMT or CP and cardiovascular events in patients with stable CAD; however, the diagnosis of angina was clinical[14]. Petersen et al. identified CP as a predictor of mortality in cardiological patients, but only

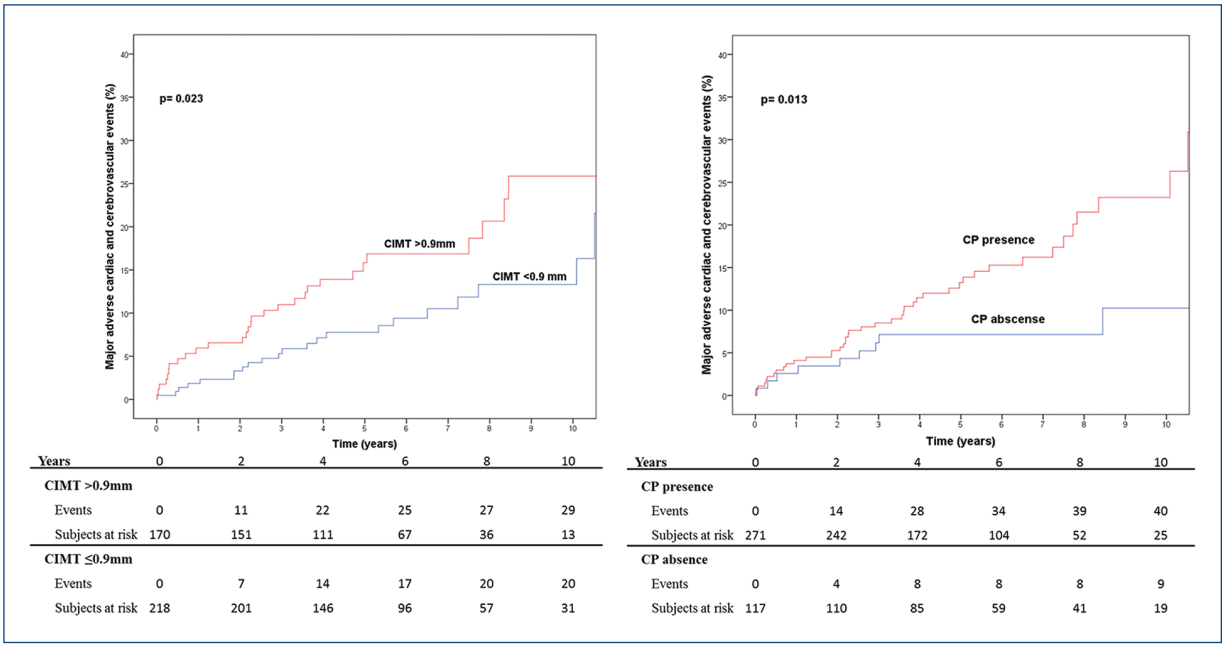

Figure 1. Cumulative incidence of major adverse cardiac and cerebrovascular events depending on carotid ultrasound characteristics (carotid plaque or carotid intima-media thickness > 0.9 mm).

Table 3. Multivariate analysis of MACCE

Variable	HR	95% CI	*p* value
Smoking habit	2.51	1.36-4.62	0.003
GFR	0.98	0.97-0.99	0.043
Aortic stenosis	2.99	1.24-7.21	0.014
Incomplete/no revascularization	1.97	1.06-3.67	0.033
Nitrates treatment	1.73	0.95-3.18	0.075
Insulin treatment	2.63	1.30-5.31	0.006
CP	2.36	1.02-5.44	0.044

CI: confidence interval, HR: hazard ratio, rest of abbreviations as in table 1 and 2, MACCE: major adverse cardiac and cerebrovascular events, GFR: glomerular filtration rate, CP: carotid plaque.

64% of them were ischemic and they did not take into account the approach done (invasive or medical treatment)[15]. Sirimarco et al. also identified CP as an independent predictor of coronary events in patients with atherosclerosis and/or CAD. CAD was defined as stable angina, previous MI or history of unstable angina, PCI or CABG but there was no angiographic assessment of CAD[16].

Studies involving patients with CAD assessed by angiography showed consistent results; however, significant CAD and end points definitions were heterogeneous. Komorovsky identified echogenic or calcified CP as a predictor of cardiac death, nonfatal MI or unstable angina in patients with acute coronary syndrome. Both, selection criteria of the subjects and definition of significant CAD (≥ 70% luminal narrowing) were different from our study[17]. Zielinski et al. and colleagues showed CIMT as a predictor of death and MACCE, defined as death, stroke or MI, in hypertensive patients with CAD defined as ≥ 50% stenosis[18]. Park found CP as a predictor of cardiac death, stroke or MI in a cohort of patients with significant CAD (defined as stenosis > 50%). Contrary to our study all patients had significant CAD, they did not evaluate the impact of medical intervention and they included stent restenosis and target vessel revascularization in the end point, not only coronary atherosclerosis progression[19]. Finally, Steinvil et al. identified carotid atherosclerosis as a predictor of all-cause mortality, MI, stroke, and any CAD revascularization in patients with any coronary stenosis > 70% but not in patients without CAD. Similar to the park, medical treatment was not systematically registered, and significant CAD definition was different from ours[20].

Pathological studies indicate that CIMT mainly represents medial hypertrophy, whereas CP probably represents a later atherogenesis stage[1-3,25-27,30]. According to this theory, CP might identify a subgroup of people with more diffuse and greater progression of atherosclerotic disease despite secondary prevention measures.

Besides CP, smoking habit, GFR, aortic stenosis, incomplete or no revascularization, and insulin treatment were MACCE predictors. Insulin treatment could reflect a subgroup of more advanced diabetes mellitus with severe organ damage or metabolic memory phenomenon[31,32]. It is not surprising to found aortic stenosis as a MACCE predictor. Aortic stenosis and CAD share physiopathological mechanism[33] and furthermore, previous studies have shown similar results[34]. Several studies have correlated chronic kidney disease[35,36] and smoking habit[36-38] to cardiovascular events and incomplete revascularization to worse prognosis in patients with ischemic heart disease[22,39]. Although left ventricular ejection fraction has been well recognized as one of the most powerful indicators of adverse prognosis,[22,40] we did not find significant association in our study. The reason could be because only 34 (8.7%) patients had mid-range and 8 (2.1%) reduced left ventricular ejection fraction. Finally, patients without CAD and previous vascular disease have an excellent prognosis.

The study has some drawbacks: it is a retrospective single institution study with low recruitment rate and therefore it is hampered by the use of different equipment and methods of image storage and new therapeutic devices or treatments that could have influenced in the final results. Due to the fact that the number of patients without previous vascular disease submitted to treadmill exercise stress echocardiography and coronary angiography yearly is low, one possible solution could be to perform a multicenter prospective study. Second, the CAD stenosis percentage was assessed visually and not using more accurate tools (intravascular ultrasound or optical coherence tomography) or by physiological assessment of CAD stenosis in the cardiac catheterization laboratory (fractional flow reserve). This is also a consequence of a retrospective study design (some techniques were not available at the time of the angiography performance) and reflects the usual clinical practice in catheterization laboratories where intermediate stenosis are treated if there is evidence of ischemia in previously performed stress test and the methods mentioned above are seldom used in case of negative stress test or at the interventional cardiologist criteria in case of no prior stress test available.

Conclusions

CP is an independent predictor of future MACCE in patients undergoing coronary angiography. The subgroup of patients without CAD and previous vascular disease has an excellent prognosis. CP presence could justify a more aggressive therapeutic approach in primary and secondary prevention.

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Conflicts of interest

The authors declare that they have no competing interest.

Ethical disclosures

The study has been approved by the Regional Ethics committee: *"Comité Territorial de Ética de Investigación de Santiago-Lugo"* with the committee's reference number 2015/270, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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