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Original article

Utilization of Evidence-based Cardiovascular Therapies and Achievement of Therapeutic Goals in Patients With Peripheral Artery Disease

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ABSTRACT

Introduction and objectives: Patients with peripheral artery disease have a high risk of cardiovascular events and death. The rate of prescription of evidence-based cardiovascular therapies and the attainment of therapeutic goals in this population is suboptimal. There are no previous studies evaluating the rate of prescription of these therapies in our country.

Methods: PERIFERICA is a cross-sectional study conducted from May to December 2009 in 440 outpatient clinics of general practitioners, internal medicine, cardiology, vascular surgery, endocrinology, and nephrology specialists throughout Spain. Subjects were included if they were aged ≥45 years and had peripheral artery disease and a blood sample obtained during the previous 6 months. Patients were excluded if they had coronary or cerebrovascular diseases. Clinical and anthropometric variables and blood analysis were obtained in all participants.

Results: In total, 4087 patients were included in the study (mean age, 68 years; 74% men). There was a high prevalence of diabetes (50%) and hypertension (90%); 79% of participants received lipid-lowering drugs (76% statins), 85.5% antihypertensive drugs (66% renin-angiotensin blockers) and 83% antithrombotics (75% antiplatelet drugs and 11% anticoagulants). In addition, 30% of subjects had a low-density lipoprotein cholesterol concentration n<100 mg/dL, 29.5% had optimal control of blood pressure, and 74.5% did not smoke. Only 8% had a good control of all of their cardiovascular risk factors.

Conclusions: Although a high percentage of subjects with peripheral artery disease receives adequate treatment with evidence-based preventive therapies, the percentage of subjects with good control of all their risk factors is low.

Utilización de tratamientos cardiovasculares preventivos y consecución de objetivos terapéuticos en pacientes con enfermedad arterial periférica

Palabras clave:
Enfermedad arterial periférica
Factores de riesgo
Inhibidores de la enzima de conversión de la angiotensina
Aterosclerosis
Tabaquismo

RESUMEN

Introducción y objetivos: Los pacientes con enfermedad arterial periférica tienen un elevado riesgo de complicaciones cardiovasculares y muerte. Sin embargo, la utilización de tratamientos cardiovasculares preventivos y la consecución de objetivos terapéuticos en esta población es subóptima. No existen datos que permitan conocer cuál es la tasa de utilización de este tipo de fármacos en nuestro país.

Métodos: PERIFERICA es un estudio transversal, realizado de mayo a diciembre de 2009 en 440 consultas de atención primaria, medicina interna, cardiología, cirugía vascular, endocrinología y nefrología, repartidas por todo el territorio nacional. Se incluyó a pacientes de 45 o más años, con enfermedad arterial periférica y una analítica sanguínea realizada durante los últimos 6 meses. Se excluyó a los sujetos con enfermedad coronaria o cerebrovascular. Se recogieron diversas variables clínicas, antropométricas y analíticas y el tratamiento recibido.

Resultados: Se incluyó a 4.087 pacientes (media de edad, 68 años; el 74% varones). La prevalencia de diabetes (50%) e hipertensión arterial (90%) era muy elevada. El 79% recibía tratamiento hipolipemiante (el 76%, estatinas); el 85,5%, antihipertensivo (el 66%, bloqueadores del sistema renina-angiotensina), y el 83%, antitrombóticos (el 75%, antiagregantes y el 11%, anticoagulantes). Un 30% tenía el colesterol unido a lipoproteínas de baja densidad < 100 mg/dl; el 29,5% tenía controlada la presión arterial y el 74,5% no fumaba. Tan sólo un 8% tenía controlados estos tres factores de riesgo cardiovascular.

Conclusiones: A pesar de que existe un elevado número de pacientes con enfermedad arterial periférica que reciben tratamiento mediante fármacos con evidencias sobre la reducción de complicaciones cardiovasculares, el porcentaje de dichos pacientes que alcanza objetivos terapéuticos es muy bajo.

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Abbreviations

LDL-C: low-density lipoprotein cholesterol
PAD: peripheral artery disease

INTRODUCTION

The prevalence of peripheral artery disease (PAD) in industrialized countries is high, and is expected to increase as the population ages.[1,2] In Spain the population prevalence of PAD in individuals older than 55 years is 8.03%.[3] Various studies have shown that patients with PAD have a high risk of coronary complications and death[4] and that the ankle-brachial index may help improve the prediction of cardiovascular risk.[5] Consequently, in patients with PAD this is considered as an equivalent of coronary disease[6,7] and, therefore, aggressive preventive therapy should be prescribed to reduce their high cardiovascular risk. Various clinical guidelines recommend that this population receive antiplatelet therapy and attain certain therapeutic goals to control their cardiovascular risk factors. In particular, the guidelines recommend statin therapy to reduce the low-density lipoprotein cholesterol (LDL-C) concentration to below 100 mg/dL, control of blood pressure with differing targets depending on the presence of other comorbidities, and treatment with drugs that block the renin-angiotensin system.[8–11]

Numerous studies have assessed the extent to which these treatments are prescribed and the therapeutic goals are attained in patients with established coronary disease[12,13] as well as their relationship to the decrease in cardiovascular morbidity and mortality.[14] However, few studies have assessed the rates of prescription in patients with PAD,[15] and even fewer have looked at the data in Spain.[16]

The aim of this study was to evaluate the rate of evidence-based prescription to reduce cardiovascular risk and the extent to which cholesterol and blood pressure targets are achieved in a broad sample of Spanish patients with PAD but no associated coronary or cerebrovascular disease.

METHODS

PERIFERICA is a cross-sectional, observational epidemiologic study conducted in outpatient clinics staffed by primary care, internal medicine, vascular surgery, and other specializations that usually see patients with PAD, such as cardiology, endocrinology, and nephrology. Each investigator was asked to include 10 consecutive patients aged ≥45 years, with documented clinical diagnosis of PAD (ankle-brachial index<0.9 with or without clinical symptoms of intermittent claudication, lower limb amputation due to chronic ischemia, or a previous revascularization procedure at this level) and a blood workup that included lipid and lipoprotein concentrations in the previous 6 months. The study excluded patients with a history of coronary disease (angina, myocardial infarction, or revascularization procedure) and/or cerebrovascular disease (stroke, transient ischemic attack, or cognitive deterioration of possible vascular origin), subjects with uncontrolled hypothyroidism, and patients with any serious or terminal illness.

A medical history was taken from all participants, and all participants underwent a physical examination that included measurements of weight, height, waist circumference, and blood pressure measured on 3 occasions, 2 min apart.

Patients were considered hypertensive if they were taking antihypertensive drugs or blood pressure values >140/90 mmHg were recorded on 2 occasions more than 1 week apart, prior to study inclusion. Diabetes mellitus was diagnosed according to the American Diabetes Association recommendations.[17] Heart failure and atrial fibrillation were diagnosed according to the patient's medical history. The estimated glomerular filtration rate was calculated using the simplified Modification of Diet in Renal Disease study equation.[18]

For this study, well-controlled blood pressure was considered to be <130/80 mmHg in patients with diabetes, acute heart failure, or glomerular filtration rate<60 mL/min/1.73 m^2, and <140/90 mmHg in the rest of the population. Target bloodwork was considered to be LDL-C<100 mg/dL, high-density lipoprotein cholesterol (HDL-C)>40 mg/dL in men and >45 mg/dL in women, and triglycerides<150 mg/dL. Control of all risk factors was considered to be optimal if the therapeutic goals for blood pressure and LDL-C had been reached and the patient did not smoke.

Statistical Analysis

The quantitative variables were compared by the single-factor ANOVA test in the case of normal distribution or by the Kruskall-Wallis H test if the parametric assumptions were not met. The discrete variables were compared by the χ^2 test.

In order to evaluate factors associated with control of the risk factors, a forward stepwise logistic regression model was used. In this model, all factors associated with control and all clinically relevant variables were introduced in the univariate model.

Statistical significance was set at $P<.05$. The statistical analysis was performed using SPSS V17.0.

The study was approved by the ethics committee of Hospital Carlos III in Madrid.

RESULTS

From May to December 2009, 440 doctors included a total of 4321 patients, of whom 234 (5.4%) were excluded because they failed to meet at least 1 inclusion criterion, yielding a total of 4087 (94.6%) assessable subjects. Patient data were collected from all autonomous communities except the Autonomous City of Ceuta and the Autonomous City of Melilla. Andalusia (16.1%), Catalonia (15.6%), the Valencian Community (12%), and the Community of Madrid (10%) were the regions with the highest number of participants. Most participants were from primary care clinics (56.5%), followed by outpatient clinics (22% internal medicine, 9.4% vascular surgery, 7.7% cardiology, and 4.5% endocrinology or nephrology).

The prevalence of risk factors was very high (Table 1). Half the participants had diabetes, with a mean disease history of 10.6 years; the estimated glomerular filtration rate was 30-60 mL/min/1.73 m^2 in 26.3% of participants and <30 mL/min/1.73 m^2 in 2.4%.

The mean age at the time of PAD diagnosis was 63.2 years; 15.4% had a history of revascularization (surgical in two thirds and endovascular in one third) and 8.4% had undergone amputation of some kind (minor in 5.4%; major in 3%).

Follow-up of Recommendations and Rate of Evidence-based Prescription

A total of 71% of patients reported some kind of daily physical activity, 38.1% for less than 30 min and 33% for more than 30 min.

Table 1
Clinical Characteristics and Analytical Results in the 4087 Assessable Study Participants

Variable	Total (n=4087)	Men (n=3016)	Women (n=1071)	*P*
Hypertension, %	89.5	87.6	92.2	<.010
Current smoker, %	25.5	30.1	12.5	<.001
Ex-smoker, %	48.9	61.7	13	<.001
Diabetes mellitus, %	50.5	49.3	54.3	<.050
Heart failure, %	12.6	11.7	15.5	<.001
Atrial fibrillation, %	12.6	11.4	16.1	<.001
Body mass index	28.8 (4.4)	28.5 (4.1)	29.4 (5)	<.001
Systolic blood pressure, mmHg	138.7 (16)	138.3 (16)	139.8 (16)	<.010
Diastolic blood pressure, mmHg	80.1 (11)	79.9 (11)	80.5 (11)	.100
Fontaine stages, %				<.001
Stage I (asymptomatic)	12.4	10.3	17.9	
Stage IIa (claudication at >150 m)	52	52.5	50	
Stage IIb (claudication at <150 m)	27	28.7	22.8	
Stage III (rest pain)	3.9	3.6	4.6	
Stage IV (ulcers or gangrene)	4.8	4.8	4.5	
Cholesterol, mg/dL	198 (44)	195 (44)	206 (43)	<.001
Triglycerides, mg/dL	156 (93)	159 (94)	155 (88)	.240
LDL-C, mg/dL	119 (36)	117 (36)	125 (37)	<.001
HDL-C, mg/dL	48.1 (13)	46.8 (13)	51.7 (13)	<.001
Estimated glomerular filtration rate, mL/min/1.73 m^2	74.5 (36)	78 (39)	64.5 (22)	<.001
Blood glucose, mg/dL	120 (42)	120 (42)	121 (44)	.250
Glycohemoglobin in diabetics, %	6.6 [5.9-7.5]	6.6 [5.8-7.4]	6.8 [6-7.5]	.980

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Unless otherwise specified, the data are expressed as mean (standard deviation) or median [interquartile range].

Lipid-lowering drugs were prescribed to 79.1%; of these, 76.2% were receiving statins and 11.4% other lipid-lowering drugs. A total of 83.4% were receiving antithrombotics (75.4% antiplatelets and 10.8% anticoagulants). Antihypertensive drugs were used by 85.5%; 66% were receiving a renin-angiotensin blocker, 36.8% diuretics, 33.5% calcium antagonists, 9.9% beta blockers, and 6.6% other antihypertensives. A total of 36.2% were taking oral hypoglycemic drugs and 18.7% were receiving insulin. Up to 45% were taking some drug for claudication.

Control of Risk Factors

Blood pressure was controlled in 29.5% of participants, and bloodwork targets had been attained for LDL-C by 30.4%, for HDL-C by 69.6%, and for triglycerides by 54.2%. Only 13% of participants had adequate control of all 3 lipid variables.

Among patients with diabetes mellitus, 24% had glycohemoglobin<6.5% and 43.2% had a level <7%.

Because 25.5% were active smokers, only 7.9% of all participants had optimal control of all risk factors (ie, blood pressure and LDL-C on target) and were not actively smoking.

Factors Associated With Control of the Risk Factors

Analyses were performed to evaluate the factors associated with control of each risk factors alone and control of the risk factors as a whole.

Control of Low-density Lipoprotein Cholesterol

The factors associated with adequate LDL-C control (Table 2) were diabetes, Fontaine stage I, and care from a medical specialist. Conversely, LDL-C was more poorly controlled in women and active smokers. The percentage of patients with LDL-C on target did not depend on lipid-lowering prescription (LDL-C<100 mg/dL in 30.5% of patients with prescription and 30.1% without prescription; *P*=.796).

Control of Blood Pressure

Blood pressure control was better (Table 3) in the oldest patients and in patients with high school or university studies. In contrast, control was worse in patients with acute heart failure or low glomerular filtration rates, groups in which the targets for good control were stricter. The percentage of patients with good control was higher among subjects not receiving antihypertensives (37.7% vs 28.1%; *P*<.001).

Control of Risk Factors as a Whole

The factors associated with optimal control of all risk factors (blood pressure, LDL-C, and no smoking) were advanced age, patients under the care of specialists other than general practitioners (usually an endocrinologist or nephrologist), higher educational level, atrial fibrillation, and daily physical exercise (Table 4). On the other hand, a history of hypertension lowered the possibilities of optimal control.

DISCUSSION

Subjects with PAD have a high rate of cardiovascular complications and death.[4] In these patients, the use of antiplatelet drugs, statins, and renin-angiotensin blockers has been associated

Table 2
Factors Associated With Poor Low-density Lipoprotein Cholesterol Control. Multivariate Analysis

	AOR (95%CI)	*P*
Female sex	1.40 (1.16-1.69)	.001
Attending specialist (reference, primary care)		<.001
Internal medicine	0.62 (0.51-0.75)	<.001
Vascular surgery	0.47 (0.36-0.61)	<.001
Other	0.37 (0.26-0.53)	<.001
Cardiology	0.99 (0.72-1.37)	.963
Active smoker	1.71 (1.40-2.09)	<.001
Diabetes mellitus	0.66 (0.56-0.77)	<.001
Fontaine (reference, stage I)		<.001
IIa	1.27 (0.98-1.65)	.071
IIb	1.39 (1.05-1.84)	.022
III	2.22 (1.34-3.68)	.002
IV	0.77 (0.51-1.16)	.209

95%CI, 95% confidence interval; AOR, adjusted odds ratio.
The variables included in the model as clinically significant in the univariate analysis were age, sex, medical specialization of the attending physician, smoking, diabetes mellitus, history of revascularization surgery or amputation, Fontaine stage, and glomerular filtration rate. The variables included as clinically relevant were educational level and lipid-lowering and antihypertensive therapy.

Table 4
Factors Associated With Not Achieving Optimal Control of Cardiovascular Risk Factors (Blood Pressure, Low-density Lipoprotein Cholesterol, and Nonsmoker). Multivariate Analysis

	AOR (95%CI)	*P*
Age	0.96 (0.95-0.98)	<.001
Attending specialist (reference, primary care)		.042
Internal medicine	0.79 (0.56-1.11)	.177
Vascular surgery	0.78 (0.49-1.22)	.275
Other	0.43 (0.25-0.75)	.003
Cardiology	0.89 (0.52-1.51)	.671
Educational level (reference, no studies)		.014
Primary	0.96 (0.67-1.38)	.838
Secondary/high school	0.81 (0.53-1.24)	.337
University studies	0.44 (0.26-0.76)	.003
Hypertension	1.58 (1.14-2.19)	.005
Atrial fibrillation	0.68 (0.47-0.98)	.040
Daily physical exercise	0.60 (0.43-0.85)	.004

95%CI, 95% confidence interval; AOR, adjusted odds ratio.
The variables included in the model as clinically significant in the univariate analysis were age, sex, medical specialization of the physician attending the patient, educational level, diabetes mellitus, hypertension, atrial fibrillation, history of revascularization surgery or amputation, Fontaine stage, physical activity, and glomerular filtration rate. The variables included in the model as clinically relevant were heart failure and lipid-lowering and antihypertensive therapy.

with better prognosis,[19,20] even though the rate of prescription is lower than recommended.[15] Most studies that evaluated their use, however, were carried out many years ago, at a time when PAD was not so widely accepted as a predictor of coronary risk as at present and the rate of evidence-based prescription for cardiovascular prevention was scant, even in patients with established coronary disease.[12] In addition, all previous studies included patients regardless of whether they presented clinical manifestations in another vascular territory or not. This could explain why preventive treatment was prescribed for coronary or cerebral arteriosclerosis rather than peripheral arteriosclerosis. Our data show that during 2009 the prescription of antithrombotic drugs, lipid-lowering drugs, and renin-angiotensin blockers in patients with PAD in Spain was high, but could have been better. The use of statins was higher than that observed in participants with PAD included in the REACH study,[16] a fact of particular relevance because our study included no patients with known vascular disease in any other territory, in order to better estimate the role attributable to PAD in the use of preventive resources. The use of these drugs in 2009, however, did not differ noticeably from that observed in coronary patients in 2005.[12]

Table 3
Factors Associated With Poor Blood Pressure Control. Multivariate Analysis

	AOR (95%CI)	*P*
Age	0.99 (0.98-0.99)	.002
Educational level (reference, no studies)		<.001
Primary	0.91 (0.75-1.11)	.353
Secondary/high school	0.70 (0.56-0.88)	.002
University studies	0.53 (0.39-0.73)	<.001
Heart failure	1.73 (1.34-2.23)	<.001
GFR (reference, GFR>90 mL/min/1.73 m^2)		<.001
60-89	1.25 (1.04-1.50)	.016
30-59	2.96 (2.33-3.75)	<.001
<30	1.64 (0.98-2.76)	.061

95%CI: 95% confidence interval; AOR: adjusted odds ratio; GFR: glomerular filtration rate.
The variables included in the model as clinically significant in the univariate analysis were age, sex, medical specialization of the physician attending the patient, educational level, physical activity, diabetes mellitus, heart failure, and glomerular filtration rate. The variables included in the model as clinically relevant were hypertension, atrial fibrillation, Fontaine stage, and antihypertensive therapy.

The high prescription rate for lipid-lowering drugs is in contrast to the low percentage of patients with optimal LDL-C control. This percentage is similar to the one observed in other studies that have assessed the degree of control in patients with coronary disease,[12] and somewhat lower than that seen in recent studies conducted in high-risk patients.[21] Several reasons could explain this low rate of patients who meet the therapeutic goals. In addition to the 21% of patients not receiving lipid-lowering drugs, the use of statins with little potency or at suboptimal doses could produce a lower decrease than necessary. Another factor that can make it difficult to reach the goals is poor therapeutic adherence. Numerous studies have shown that a very significant percentage of patients discontinue statin therapy rapidly. This occurs more often in patients in primary prevention than in subjects who have already had a coronary complication,[22] probably due to greater awareness among coronary patients of the importance of controlling risk factors to avoid a new event. The data suggest that subjects with PAD are not aware of the severity of the diagnosis. In any case, the problem does not appear to be a lack of therapeutic alternatives, as 70% failed to meet the targets but only 3% were taking 2 or more lipid-lowering drugs.

The factors associated with worse LDL-C control were female sex and active smoking, whereas diabetes and care from a specialist were associated with better control. Women were just as likely as men to use lipid-lowering drugs (data not shown), although women had a higher mean LDL-C, indicating that lower doses of lipid-lowering drugs were administered or the baseline cholesterol concentrations were higher. The latter is likely, if we consider that women have a lower prevalence of arteriosclerosis,

and a greater burden of risk factors (eg, hypercholesterolemia) is needed for this disease to develop. Smoking is probably a marker of therapeutic noncompliance or medical inertia in patients who fail to cooperate in the control of their risk factors. Diabetics tend to have a normal LDL-C concentration, which is no different than that of the general population, and therefore it is presumably easier to lower their LDL-C to below 100 mg/dL with lipid-lowering therapy.

The percentage of patients with adequate blood pressure control was also low, very similar to that found in other studies performed among populations with PAD.[16] The percentage of well-controlled patients was higher in those who were older and had higher educational levels. Subjects with acute heart failure and renal failure required stricter blood pressure targets, and this was probably the reason for worse control among these patients. The study had conflicting results concerning the relationship between age and blood pressure control. In general, therapeutic compliance tends to be better at older ages, although some studies have shown that blood pressure control is better in older persons even after correcting for adherence to treatment.[23]

Optimal control of all cardiovascular risk factors was only seen in 7.9% of subjects. Patients who were older, had university studies, and did physical exercise (all markers associated with better treatment adherence), and those with atrial fibrillation had better control. Conversely, patients with hypertension or under the care of a general practitioner had worse control. It has recently been shown that most of the decrease in the coronary mortality rate observed in the past few years in Spain is attributable to better control of risk factors and the evidence-based prescription for cardiovascular prevention.[24] Therefore, it is important to identify patient characteristics associated with optimal control of risk factors.

Limitations

The present study had several limitations. First of all, the choice of physicians was not randomized. Hence, it may not be possible to extrapolate patient control or drug type to other physicians in Spain. Our data were insufficient to determine the reasons why the goals were not usually attained, despite a high level of prescription of preventive drugs. The study did not consider if this could be due to low adherence or to suboptimal use of therapeutic resources. However, no studies have evaluated such a large sample of patients with PAD and without vascular disease in other territories.

CONCLUSIONS

We concluded that the percentage of patients with PAD but no vascular manifestations in any other area who are receiving preventive treatment is high. However, the percentage of patients who reach the therapeutic goals is low. New studies are needed to determine if the low rate of attainment of therapeutic goals is due to low adherence or suboptimal use of treatment.

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CONFLICTS OF INTEREST

Dr. J.M. Mostaza, Dr. E. Puras, and Dr. M. Blasco state that they have received fees for consulting and for forming part of the PERIFERICA study coordinating committee.

Statisticians from the pharmaceutical company analyzed the data but did not participate in the discussion of the results or the writing of the present paper.

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