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Incidence and risk factors for non-traumatic amputation of lower limbs in patients on hemodialysis

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SUMMARY

Background and aims: *The purpose of this study was to assess the incidence and risk factors for non-traumatic lower extremity amputation (LEA) in patients on haemodialysis (HD).*

Methods: *We investigated our HD population attending our clinic between Jan 1988 and Dec 2002, who had had LEA. Uni- and multivariate analyses were used to determine association of LEA with demographic characteristics such as diabetes, hypertension, smoking, myocardial infarction, stroke, dyslipidaemia, haematocrit, urea, creatinine, calcium, phosphorous, parathyroid hormone (PTH) and albumin levels.*

Results: *Of 516 patients, 20 (3.9%) underwent 32 amputations; 21 major and 11 minor. The incidence was 1.1 amputees/100 p-years. There were 11 (10.8%) diabetics and 9 (2.2%) non-diabetics; incidence of 4.2 and 0.6 amputees/100 p-years, respectively. Non-diabetic amputees were older than non-amputees: 68.9* vs *58.2 years (p = 0.013) and had been on HD longer: 71.4 ± 44* vs *42 ± 37 months (p = 0.019). There were 60% deaths within the first year of amputation and the causes were 60% cardiovascular. Univariate analysis indicated significant association of LEA with ageing, diabetes, smoking, myocardial infarction, stroke, high cholesterol, and low PTH levels. Multivariate Cox regression identified independent associations of amputation with diabetes, previous myocardial infarction and stroke and/or transient ischaemic attack.*

Conclusions: *The incidence of LEA in HD patients is very high and is associated with diabetes and previous cardiovascular events. Advanced age and longer time on HD are factors related to LEA in non-diabetics. With increasing numbers of diabetics and older people on HD, new strategies are needed for peripheral arterial disease management so as to avoid its progression to critical ischaemia.*

Key words: ***Lower extremity amputation. Risk factors. Peripheral arterial disease. Haemodialysis.***

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INCIDENCIA Y FACTORES DE RIESGO DE AMPUTACIÓN NO TRAUMÁTICA DE MIEMBROS INFERIORES EN LOS PACIENTES EN HEMODIÁLISIS

RESUMEN

A pesar de la alta prevalencia de enfermedad cardiovascular en los pacientes en hemodiálisis (HD), la incidencia de amputación de miembros inferiores (MMII) es poco conocida.

***Objetivo:** Analizar incidencia y factores condicionantes de amputación no traumática de MMII en los pacientes en HD.*

Métodos: *Analizamos los pacientes incluidos en HD de 1/1/88 a 31/12/02 e identificamos amputados y amputaciones efectuadas. Realizamos análisis uni y multivariante de la asociación de amputación con edad, sexo, tiempo en HD, historia de diabetes, hipertensión arterial, infarto de miocardio (IM), accidente cerebrovascular (ACV), tabaquismo y niveles de colesterol, triglicéridos, hematocrito, urea, creatinina, calcio, fósforo, PTH y albúmina.*

***Resultados:** Se incluyeron 516 pacientes (59,5 ± 17 años, 102 diabéticos), tiempo en HD 40,15 ± 37 meses, seguimiento de 1.726 pacientes-año. Veinte (3,9%) sufrieron una o varias amputaciones, con incidencia de 1,1 paciente amputados/100 p-año. Once (10,8%) eran diabéticos, incidencia 4,2 amputados/100 p-año. Nueve (2,2%) no diabéticos, con 0,6 amputados/100 p-año. Las amputaciones fueron 32: 21 mayores (supra e infracondíleas) y 11 menores (pies y dedos). El 60% falleció al año de su primera amputación y las causas de muerte fueron cardiovasculares en el 60% de los casos. En el análisis univariante los amputados tenian mayor edad, presencia de diabetes, tabaquismo, antecedentes de IM y ACV, colesterol y menor PTH. En el multivariante, diabetes: OR: 5,9 (IC 95%: 2,4-16, p = 0,000), IM: OR: 7,2 (IC 95%: 2,1-24,7, p = 0,002) y ACV: OR: 4,8 (IC 95%: 1,3-17, p = 0,015), se asociaron de forma independiente con el riesgo de amputación.*

***Conclusiones:** La incidencia de amputación de MMII en los pacientes en HD es elevada. Factores de riesgo conocidos como diabetes y patología cardiovascular aterosclerótica establecida son condicionantes de amputación. La creciente inclusión en HD de pacientes diabéticos y de edades avanzadas hace previsible el aumento de arteriopatia periférica lo que hace necesario planificar estrategias que prevengan su aparición y progresión a isquemia crítica.*

Palabras clave: ***Amputación de miembros inferiores. Hemodiálisis. Factores de riesgo.***

INTRODUCTION

It is known that in the general population the rate of lower limb amputation varies according to geographic localization and race[1-3].

The natural course of peripheral arterial disease in patients with intermittent arterial claudication entails a high risk for myocardial infarction and of surgery of the lower limbs and amputation that may reach 12% at three months of onset of resting pain of the limb, ulceration and gangrene[4]. The presence of peripheral arterial disease increases the risk of death from cardiovascular disease by 3 to 6 fold in the asymptomatic cases and by 15 fold in severe cases[5].

In spite of the high prevalence of cardiovascular disease in hemodialysis patients, the incidence of lower limb amputation has remained unknown until the recent publication of an epidemiological study on patients with renal function replacement therapy. This study shows a high incidence of lower limb amputation for non-traumatic causes in dialysis patients of the U.S. Medicare Program[6].

To date, no study has been published that analyzes the incidence and risk factors for amputation of the lower limbs in the population on hemodialysis in Southern Europe, a geographical area where there is a low prevalence of cardiovascular disease in the general population[7-9].

The aim of our study was to analyze the incidence and conditioning factors for non-traumatic amputation of the lower limbs in hemodialysis patients.

METHODS

We considered patients with chronic renal failure that started hemodialysis replacement therapy in our Center (including a hospital unit and two peripheral centers), from 01/01/1988 to 12/31/2002, and that remained with this technique for at least one month. Patients that had initiate therapy in another center, those whose usual treatment had been CAPD, those had had received previous renal transplantation, or those that had recovered enough renal function to withdraw from dialysis were excluded. The observation period was that comprised between the onset of replacement therapy to end of it for transplantation, CAPD, death or end of study at 01/31/2003.

We identified amputated patients and lower limb amputations performed excluding those for traumatic, neoplasic or vasculitic causes. We considered major amputation the one performed at an infracondylar, below the knee joint, or supracondylar, more proximal, and minor amputation the one performed at the foot or more distally.

We examined those variables that could be related to the risk of having peripheral arterial disease. We included demographic factors such as age at onset of dialysis, gender, and time on replacement therapy. Also included were the presence of diabetes, arterial hypertension, ischemic heart disease, cerebrovascular stroke, and cigarette smoking, together with analytical parameters such as total cholesterol, triglycerides, hematocrit, urea, creatinine, calcium, phosphorus, intact PTH, and albumin.

We considered as diabetic patient the one that at some point of his/her clinical course would have been diagnosed with diabetes with indication of pharmacological treatment to control his/her glycemia. Arterial hypertension diagnosis prior to or after onset of replacement therapy was considered when the patient had had antihypertensive medication. As ischemic heart disease diagnosis, we considered it when performed through coronariography or by presentation of myocardial infarct diagnosed by means of the clinical picture, and enzymes and electrocardiogram changes. Diagnosis of cerebrovascular stroke or transient ischemic attack was considered when it was already established in the patient's history or during the follow-up period by checking it by imaging tests or by a neurologist's report.

According to cigarette smoking use, patients were categorized as never smokers and smokers, the latter comprising both on active smoking and those withdrawing from smoking within the last ten years prior to the study beginning.

The analytical parameters were the ones corresponding to the check-up performed within weeks 5 and 10 after starting of hemodialysis. The hematocrit and biochemistry data were determined with an auto-analyzer and PTH by immunochemoluminescence, Ciba-Corning, Medfield, MA (NV: < 65 pg/mL).

Statistical analysis

A univariate analysis was done by the Student's t test for non-paired quantitative variables, and χ^2 for qualitative variables, obtaining the relative risk and 95% confidence intervals. For multivariate analysis Cox's logistic regression analysis was done, and odds ratios and 95% confidence intervals were obtained. Kaplan-Meier curves were used for survival analysis and the log-rank test to compare the curves between amputated and non-amputated patients. A p value < 0.05 was considered statistically significant. All the analyses were performed with the statistical package SPSS 11.0.

RESULTS

Characteristics of the population included

Between 01/01/1988 and 12/31/2002, 702 patients on replacement therapy were included. After exclusions, included patients totaled 516. The considered population had the following characteristics: age 59.5 ± 17 years (range: 14.6-89.3 y.); gender, 288 (55.8%) men; time on dialysis 40.15 ± 37 months (range: 1.07-183.4 m.). Follow-up: 1726 patients-year. Causes for nephropathy were: diabetes, 13.8%; nephroangiosclerosis, 8.5%; glomerulonephritis, 16.7%; interstitial, 20.3%; polycystic renal disease, 6.6%; systemic diseases, 8.1%; familial nephropathy, 3.7%; unknown, 19.4%; miscellaneous, 2.9%. According to previous mentioned criteria, 102 (19.7%) patients had been diagnosed with diabetes, of which 51 (50%) had started on dialysis since 01/01/1999. Seventeen patients transiently treated with peritoneal dialysis, generally because of vascular access difficulties, were also included in the study.

Incidence of amputated patients

Twenty (3.9%) patients were submitted to one or more lower limb amputations. They were 14 (4.9%) men and 6 (2.6%) women. The incidence was 1.1 amputated patients per 1000 patients and follow-up year, 1.4/100 men-year and 0.8/100 women-year. Eleven patients were diabetic (10.8% of diabetics), incidence of 4.2 amputated diabetics/100 p-year and nine (2.2%) were not diabetic, incidence 0.6/100 p-year. The chance of being amputated for diabetics was five fold higher than for non-diabetics (RR: 5.14). Nephropathy cause in non-diabetic amputated patients was: unknown 5, nephroangiosclerosis 2, systemic disease 1, and interstitial nephropathy due to calculi 1.

The first amputation in diabetic patients was done early. Thirty three percent of amputated diabetics had their first amputation within the first months on dialysis, and 66% within the first year. At 30 months of permanence on dialysis therapy, all amputated diabetic patients had already received their first amputation, After 30 months on dialysis, there were re-amputations in these patients but no other diabetic patient was amputated. Two non-diabetic patients suffered their first amputation within the first two years and the remaining did so from the forth year on dialysis and on. In the Kaplan-Meier survival analysis, the chance of being free from amputation at 30 months of being on dialysis was 85.6% in diabetics and 98.6% in non-diabetics (log-rank test: $p < 0.00001$).

Amputations

Indication for amputation was gangrene in 16 patients, and non-abating resting ischemic pain in four. Four patients were treated with chemical sympathectomy, three with posterior cords neurostimulation, and three with intradialysis prostaglandins for 4 weeks. Eight revascularization procedures were performed in six patients, two diabetics and four non-diabetics.

Thirty-two amputations were done, 21 (64%) major amputations, 15 supra- and 6 infracondylar. Diabetic patients were submitted to 18 amputations, 10 major amputations, and non-diabetic patients received 14 amputations, of which 11 were major amputations. Minor amputations in diabetics were eight (44.4%) and in non-diabetics were three (21.4%) ($P < 0.05$). The number of re-amputated patients was similar in both groups (5 diabetics, and 5 non-diabetics). Three patients received a major bilateral amputation (1 diabetic, 2 non-diabetics).

Factors related with amputation

In the univariate analysis, amputated patients were older, the ratio of diabetics and smokers was greater, and there was a higher number of patients with a personal history of myocardial infarction and cerebrovascular stroke or transient ischemic attack. Besides, the proportion of patients with high cholesterol and low PTH was higher (Table I). There were no differences in hematocrit, urea, creatinine, triglycerides, calcium, phosphorus, albumin, and arterial hypertension.

This analysis was separately done in diabetics and non-diabetics.

In diabetics, time on dialysis until the first amputation was shorter than the total observation time for non-amputated patients. Besides, they had lower creatinine and PTH and higher cholesterol. There was also a higher proportion of patients with previous myocardial infarction or cerebrovascular stroke or transient ischemic attack (Table II). Non-diabetic amputated patients were 10 years older than non-amputated patients, most of them were men, and time on dialysis until their first amputation was longer than total time on dialysis for non-amputated patients. Their creatinine was higher and the proportion of smokers was higher (table III).

Table I. Factors related to amputation. Univariate analysis

	Amputated N = 20	Non-amputated N = 496	Relative risk	95% CI	p
Age (years)	64.7 ± 10	59.3 ± 17	–	–	= 0.036
Diabetes	55%	18.3%	4.94	2.1-11.6	= 0.0001
Smokers	70%	41.3%	3.3	1.3-8.4	= 0.019
Myocardial infarction	25%	3.2%	7.8	3.1-19.5	= 0.001
Ischemic stroke	20%	3.6%	5.6	2-15.4	= 0.008
Cholesterol > 230 mg/dL	40%	13.7%	3.9	1.6-9.1	= 0.004
PTH (pg/mL)	138.6 ± 197	246.8 ± 310	–	–	= 0.028

Table II. Factors related to amputation in diabetics

	Amputated N = 11	Non-amputated N = 91	p
Time on dialysis (*)	9.4 ± 8.4	31.3 ± 29	= 0.0001
Creatinine (mg/dl)	6.01 ± 1.6	7.64 ± 2.1	= 0.016
PTH (pg/ml)	102.6 ± 62.3	262.5 ± 289.5	= 0.0001
Cholesterol (mg/dl)	239 ± 82	196 ± 63	= 0.047
Myocardial infarction	4 (36.4%)	7 (7.7%)	= 0.004
Ischemic stroke	4 (36.4%)	4 (4.4%)	= 0.0001

(*) months until the first amputation or until exit from dialysis.

Table III. Factors related to amputation in non-diabetics

	Amputated N = 9	Non-amputated N = 405	p
Age (years)	67.8 ± 9.3	57.8 ± 18	= 0.013
Gender	8 H (88.9%)	226 H (55.8%)	= 0.048
Time on dialysis (*)	71.5 ± 44	41.6 ± 37	= 0.019
Creatinine (mg/dL)	10.8 ± 3.3	8.9 ± 2.3	= 0.017
Smoker	8 (88.9%)	161 (39.8%)	= 0.003

(*) months until the first amputation or until exit from dialysis.

Table IV. Factors related to amputation. Multivariate analysis

	Odds Ratio	95% CI	p
Diabetes	5.92	2-15.9	= 0.0001
Myocardial infarction	7.2	2.1-24.7	= 0.002
Ischemic stroke	4.8	1.3-17.4	= 0.015

In the multivariate analysis, independent factors associated with amputation were diabetes diagnosis and a previous history of myocardial infarction or ischemic ictus (Table IV).

Survival and mortality

The Kaplan-Meier analysis shows the shorter survival in the amputated patient. At 20 months, survival rate is 81.3% in non-amputated patients vs. 55% in amputated patients, at 60 months, 62.2% vs. 35%, and at 120 months 33.3% *vs* 15% (log-rank test: $p < 0.0028$).

These differences only occur among diabetic patients, with a survival rate at 2 years of 71% in non-amputated vs. 18% in amputated patients, and at 5 years of 49% vs. 9%. At 80 months, all amputated diabetics had died, and 28% of non-amputated diabetics still alive (fig. 1).

Survival rate of patients after the first amputation was 15.3 ± 16% and in non-diabetics 13.2 ± 22 months (NS). Survival rate for the first major amputation was 14.5 ± 19 months and for the first minor amputation 14.1 ± 20 months (NS). Mortality rate of patients after the first amputation was 15% within the first month, 60% within the first year, and 90% within two years. All amputated patients died within the observation period.

Three patients died because of infections, and one because of cachexia. The remaining were six sudden deaths, presumably from cardiac origin, two myocardial infarctions, three cerebrovascular strokes, and one mesenteric ischemia, which means that 60% of deaths were from cardiovascular origin. In four patients, the cause of death was related to lower limbs

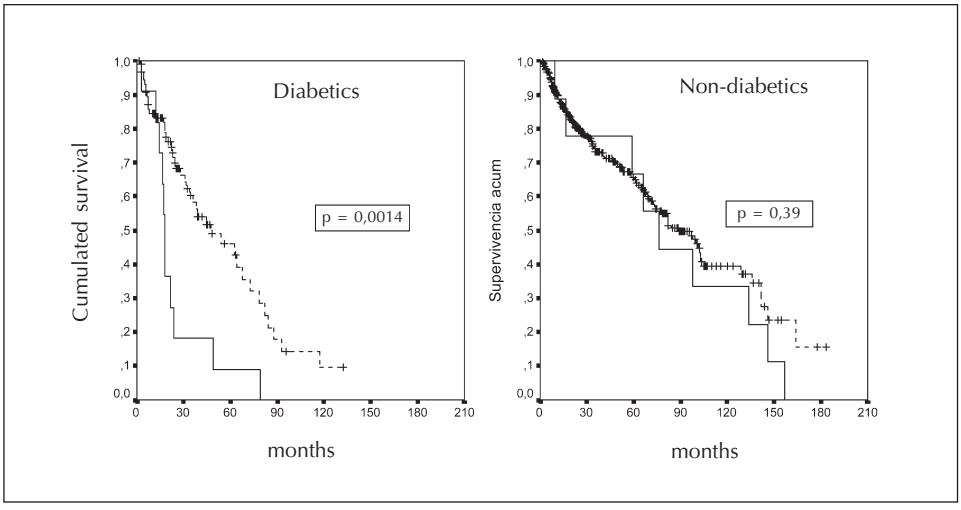

Fig. 1.—Kaplan-Meier survival curves: amputated patients, diabetics and non-diabetics. x-x amputated patients.

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gangrene, in two cases of the contralateral limb to the amputated one.

DISCUSSION

The results from the present study show a high incidence of lower limb amputation for non-traumatic causes in a large sample of patients on hemodialysis with similar characteristics to those in the Spanish dialysis population[10], in whom a prolonged follow-up has been performed.

Although high, this incidence rate is 4.5 times lower than that observed by Eggers *et al.* in dialysis patients in the U.S. Medicare Program, which rates raises to 4.9 amputations/100 patients, 13.8/100 diabetics[6]. This recent study by Eggers provides useful information since it quantitates the problem in US patients on replacement therapy. However, according to our data, these data are not inferable to the Spanish population on dialysis.

Variability in the lower limb amputation rate depending on geographical location and race is known in the general population, being the highest in North America and some communities in Northern Europe, and the lowest in Southern Europe and Asia.[1-3] The rate of 24.95 amputations per 100,000 population in the USA[11] contrasts with the 2.8 per 100,000 population rate in Spain[1,12]. This is coherent with the known lower incidence of coronary heart disease, and cardiovascular disease in general, in the Mediterranean population. Dietary habits[7], variations in risk factors such as diabetes prevalence, race, cigarette smoking[8], and other factors[9], have been implicated in these variations.

To date, there are no studies that have analyzed lower limb amputation in dialysis patients in Europe. Our results confirm that, although the risk for amputation is high for dialysis patients, the low amputation incidence in the general Spanish population is applicable to the dialysis population.

Risk factors related with amputation in our study have been the already known both in the general population and in dialysis patients: diabetes, advanced age, male gender, smoking, hypercholesterolemia, and a history of a previous cardiovascular event[4,13]. In American patients on dialysis, a high prevalence of cardiovascular risk factors has been observed with a remarkable variability in their distribution with regards to ethnic factors, as compared to the European Community[14,15].

In our analysis, diabetes increased the risk for amputation, although in a lower proportion than in the general population[16,17]. Although this lower risk increase has been previously observed[6], a sub-analysis of amputation in diabetics confirms the 3.3 lower incidence than the one in the dialysis diabetic population in the USA. This may suggest that factors other than the lower diabetes prevalence in dialysis patients in Spain account for the lower amputation incidence.

In diabetic patients, amputation was performed within the first 30 months since dialysis beginning. Amputation within early stages of replacement therapy, with the highest incidence within the first year, has been previously reported, with no clear explanation for this fact[18,19]. Although peripheral arterial disease is more prevalent in diabetics[20], amputation is more related to microangiopathy[21]. However, the greater microangiopathy prevalence in these patients may have been determinant for amputation, besides other cardiovascular events. In our study, 45% of amputates diabetics *vs* 11% of non-amputated diabetics had had a previous cardiovascular event. Besides, 82% of amputated *vs* 49% of non-amputated patients died from cardiovascular causes (data not shown). These results indicate the high prevalence of cardiovascular disease in the amputated diabetic patient, the higher incidence of cardiovascular events, including lower limb occlusive arterial disease, and the lower survival. This could explain, in part, that amputation occurs at the early stages of dialysis treatment.

Together with diabetes, other factors such as previous myocardial infarction and cerebrovascular stroke were independently associated to the risk of amputation on dialysis. The association between peripheral arterial disease and coronary heart disease and cerebrovascular disease is well known not only in the general population, in which 40% of patients with intermittent claudication have coronary heart disease[22], but also in patients with chronic renal failure, with a similar proportion[23,24].

While considering incident patients on hemodialysis with a prolonged follow-up period, our study allows the observation of an association between mortality and amputation in the diabetic patient, as it occurs in the general population[25]. Although this fact might be guessed, this association has not been shown in other studies of patients on dialysis with a cross-sectional design that has hampered the observation of patients with a shorter survival such as diabetics[14].

After the first amputation, survival was short for all patients, similarly to what has been described[26,27]. Some studies have shown a shorter survival after the first major amputation[19] and others have observed a discrete longer survival in diabetics, attributed in part to the greater rate of minor amputations in diabetic patients[6]. In our study, survival after the first ampu-

tation was similar in diabetics and non-diabetics, and for whatever amputation level. This confirms that it is the generalized atherosclerotic condition, and not local factors, what determines survival in the amputated patient. Only 20% of our patients died of causes attributable to critical lower limb ischemia. This is in agreement to what has been observed in the general population where death is rarely a direct outcome of peripheral arterial disease[5,28].

In summary, our results show a high incidence of lower limb amputation for non-traumatic causes in patients on hemodialysis. Known risk factors such as diabetes and previous cardiovascular events condition amputation. It is necessary to consider a greater use of therapies of known efficacy in the general population[29,30], although the risk-benefit ratio of these therapies in chronic renal failure is not well established so far[31-34]. Although the amputation rate found is high, it is considerably lower than that of the US dialysis population, the only reference currently. The known differences in the general population are also applicable to the dialysis population, although the lower prevalence of some risk factors does not seem to explain this difference.

REFERENCES

1. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia: The global lower extremity amputation study group: *Br J Surg* 87: 328-337, 2000.
2. Lavery LA, Ashry HR, Van Houtum W, Pugh JA, Harkless LB, Basu S: Variation in the incidence and proportion of diabetes-related amputations in minorities. *Diabetes Care* 19 (1): 48-52, 1996.
3. Rucker-Whitaker C, Feinglass J, Pearce WH: Explaining Racial Variation in Lower Extremity Amputation: a 5-Year Retrospective Claims Data and Medical Record Review at an Urban Teaching Hospital. *Arch Surg* 138 (12): 1347-1351, 2003.
4. Ouriel K: Peripheral arterial disease. *Lancet* 358: 1257-1264, 2001.
5. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D: Mortality over a period of 10 years in patient with peripheral arterial disease. *N Engl J Med* 326: 381-386, 1992.
6. Eggers PW, Gohdes D, Pugh J: Non-traumatic lower extremity amputations in the Medicare end-stage renal disease population. *Kidney Int* 56 (4): 1524-1533, 1999.
7. Serra-Majem L, Ribas L, Tresserras R, Ngo J, Salleras L: How could changes in diet explain changes in coronary heart disease mortality in Spain? The Spanish paradox. *Am J Clin Nutr* 61 (Supl. 1), 1351s-1359s, 1995.
8. ERICA Research Group: The CHD risk-map of Europe: the first report of the WHO-ERICA project. *Eur Heart J* 9 (Supl. 1): 1-36, 1988.
9. Law M, Wald N: Why heart disease mortality is low in France: the time lag explanation. *Br Med J* 318: 1471-1476, 1999.
10. Comité de Registro de la SEN: Informe de diálisis y trasplante año 2001 de la Sociedad Española de Nefrología y Registros autonómicos. *Nefrología* 24: 21-33, 2004.
11. Feinglass J, Brown JL, LoSasso A, Sohn MW, Manheim LM, Shah SJ, Pearce WH: Rates of lower-extremity amputation and arterial reconstruction in the United States, 1979 to 1996. *Am J Public Health* 89 (8): 1222-7, 1999.
12. Calle-Pascual AL, García-Torre N, Moraga I, Díaz JA, Durán A, Moñuz G, Serrano FJ, Martín-Álvarez PJ, Charro A, Marañes JP: Epidemiology of non-traumatic lower-extremity amputation in Area 7, Madrid, between 1989 and 1999. *Diabetes Care* 24: 1686-1689, 2001.
13. Moss SE, Klein R, Klein BEK: The 14-year incidence of lower-extremity amputations in a diabetic population. The Wisconsin Epidemiological Study of Diabetic Retinopathy. *Diabetes Care* 22: 951-959, 1999.
14. O'Hare AM, Bacchetti P, Segal M, Hsu ChY H, Johansen KL: Factors associated with future amputation among patients undergoing hemodialysis: results from the dialysis morbidity and mortality study waves 3 and 4. *Am J Kidney Dis* 41: 162-170, 2003.
15. Goodkin DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, Saito A, Rayner HC, Kurokawa K, Port FK, Held PJ, Young EW: Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the dialysis outcomes and practice patterns study (DOPPS). *J Am Soc Nephrol* 14: 3270-3277, 2003.
16. Siitonen OI, Niskanen LK, Leakso M, Siitonen JT: Lower-extremity amputations in diabetic and non diabetic patients. A population-based study in eastern Finland. *Diabetes Care* 16: 16-20, 1993.
17. Humphrey LL, Palumbo PJ, Butters MA, Hallett JW, Chu ChP, O'Fallon M, Ballard DJ: The contribution of non-insulin-dependent diabetes to lower-extremity amputation in the community. *Arch Intern Med* 154: 885-892, 1994.
18. McGrath NM, Curran BA: Recent commencement of dialysis is a risk factor for lower-extremity amputation in a high-risk diabetic population. *Diabetes Care* 23: 432-433, 2000.
19. Dossa CD, Shepard AD, Amos AM, Kupin WL, Reddy DJ, Elliot JP, Wilczwski JM, Ernst CB: Results of lower extremity amputations in patients with end-stage renal disease. *J Vasc Surg* 20: 14-19, 1994.
20. Murabito JM, D'Agostino RB, Silbershatz H, Wilson PWF: Intermittent claudication: a risk profile from the Framingham Heart Study. *Circulation* 96: 44-49, 1997.
21. Reiber GE, Pecoraro RE, Koepsell TD: Risk factors for amputation in patients with diabetes: a case control study. *Ann Intern Med* 117: 97-105, 1992.
22. CAPRIE Steering Committee: A randomised, blinded trial of clopidogrel *versus* aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 348: 1329-1339, 1996.
23. Stack AG, Bloembergen WE: Prevalence and clinical correlates of coronary artery disease among new dialysis patients in the United States: a cross-sectional study. *J Am Soc Nephrol* 12: 1516-1523, 2001.
24. Fishbane S, Youn S, Flaster E, Adam G, Maesaka JK: Ankle-arm blood pressure index as a predictor of mortality in hemodialysis patients. *Am J Kidney Dis* 27: 668-672, 1996.
25. Nelson RG, Gohdes DM, Everhart JE, Hartner JA, Zwemer FL, Petitt DJ, Knowler WC: Lower extremity amputations in NIDDM: 12-year follow-up study in Pima Indians. *Diabetes Care* 11: 8-16, 1988.
26. Simsir SA, Cabellon A, Kohlman-Trigoboff D, Smith BM: Factors influencing limb salvage and survival after amputation and revascularization in patients with end-stage renal disease. *Am J Surg* 170: 113-117, 1995.
27. O´Hare A, Feinglass J, Reiber GE, Rodríguez RA, Daley J, Khuri S, Henderson WG, Johansen KL: Postoperative mortality after non-traumatic lower extremity amputation in patients with renal insufficiency. *J Am Soc Nephrol* 15: 427-434, 2004.

28. Dormandy J, Heeck L, Vig S: The natural history of claudication: risk to life and limb. *Semin Vasc Surg* 2: 123-137, 1999.
29. Hiatt ER. Drug therapy: Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 344: 1608-1621, 2001.
30. McDermott MM, Guralnik JM, Greenland PH, Pearce WH, Criqui MH, Liu K Taylor L, Chan Ch, Sharma L, Schneider JR, Ridker PM, Green, Quann M: Statin use and leg function in patients with and without lower-extremity peripheral arterial disease. *Circulation* 107: 757-761, 2003.
31. Sánchez Perales MC, Vázquez E, García Cortés MJ, Borrego FJ, Borrego J, Pérez del Barrio P, Liébana A, Gil JM, Viedma G, Pérez Bañasco V. Antiagregación plaquetaria y riesgo hemorrágico en hemodiálisis. *Nefrología* 5: 456-462, 2002.
32. Vázquez E, Sánchez-Perales C, Lozano C, García Cortés MJ, Borrego F, Guzmán M, Pérez P, Pagola C, Borrego MJ, Pérez V: Comparison of prognostic value of atrial fibrillation *versus* sinus rhythm in patients on long-term hemodialysis. *Am J Cardiol* 92: 868-871, 2003.
33. Abbott KC, Trespalacios FC, Taylor AJ, Agodoa LY: Atrial fibrillation in chronic dialysis patients in the United States: risk factors for hospitalization and mortality. *BMC Nephrol* 24; 4 (1): 1, 2003.
34. Vázquez E, Sánchez Perales C, García Cortés MJ, Borrego FJ, Lozano C, Guzmán M, Gil JM, Liébana A, Pérez P, Borrego MJ, Pérez V: Ought dialysis patients with atrial fibrillation be treated with oral anticoagulants? *Int J Cardiol* 87: 135-139, 2003.