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Cardiovascular risk in hemodialysis in Spain: prevalence, management and targt results (MAR study)

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SUMMARY

Cardiovacular disease is the main cause of morbidity and mortality in hemodialysis (HD) patients. However, there are no reliable data neither on the prevalence of cardiovacular disease nor its risk factors in Spain. The Morbidity and mortality Anemia Renal study (MAR) is a two-year multicenter, open-label, prospective cohorts study. Its main objective is to assess the general morbidity and mortality, particularly of a cardiovascular cause, and its relationship with the degree of anemia. Secondary objectives are: a/ the description of current clinical practices in anemia, dialysis, vascular access, and CV risk factor management; and b/ the description of hospitalization and mortality causes. This paper describes the prevalence of cardiovascular disease and risk factors of the HD population in Spain. A total of 1710 patients were included (60% male, aged 64.4 years, 16.2 months on HD). The mean co-morbidity Charlson index was 6.5 ± 2.3. Cardiovascular disease was the most prevalent comorbidity, 16.7% had a coronary disease, and 13.9% had different degrees of heart failure, while 11.6% had arrhythmia, 1.7% stroke and 5.5% peripheral artery disease. The prevalence of hypertension was 75,8%, 74,4% of patients received antihypertensive drugs, and still 40% of patiens had an inadequate blood pressure control. The investigators considered as dyslipidemic 34.1% of patients, and prescribed treatment to 69.5% of them, while the remaining 30.5% (10.4% of the total) had hyperlipidemia with no drug therapy. Eleven percent was active smoker, and 26,6% former smoker. There was 47,4% of patients with a corporal mass index above 25. Secondary hyperparathyroidism with PTH above of 300 pg/ml was present in 22.2% of patients. Despite the EBPG and K-DOQI recommendations, only 68.8 % of prevalent hemodialysis patients attained a hemoglobin (Hb) above 11 g/dl, 89.4 % ferritin levels above 100 ng/ml, 66.5%/a a transferrin saturation index (TSI) above 20%, and 61.1% met all three objectives. In summary, this first cross-sectional analysis has allowed us to know in detail the standard practice in multiple aspects of management of HD population in Spain. It has also established clear differences in the prevalence of cardiovascular disease and risk factors from the US registries. Last but not least we have identified therapeutic opportunities to improve the course and prognosis of our patients.

Keywords: Cardiovascular risk. Hemodialisis. Anemia. Guidelines. Hipertensión. Dislipidemia.

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RIESGO CARDIOVASCULAR EN HEMODIÁLISIS EN ESPAÑA: PREVALENCIA, PAUTAS DE ACTUACIÓN Y OBJETIVOS (ESTUDIOS MAR)

RESUMEN

La enfermedad cardiovascular (CV) es la principal causa de morbimortalidad en enfermos en hemodiálisis (HD). Sin embargo no disponemos actualmente de datos sobre la prevalencia de sus diferentes manifestaciones, ni de sus factores de riesgo en la población en HD española. Morbidity and mortality Anemia Renal study (MAR) es un estudio descriptivo, prospectivo, multicéntrico y abierto de serie de casos. Su objetivo principal es la valoración de la morbilidad y mortalidad general, especialmente de causa CV, y su relación con el grado de anemia. Los objetivos secundarios son la descripción de las pautas habituales de manejo de estos pacientes y los objetivos de control alcanzados. Presentamos aquí el análisis descriptivo del riesgo CV en la población del estudio MAR. Se incluyeron 1710 enfermos prevalentes de 119 centros (60% varones, 64,4 años, tiempo en HD 15,9 meses). La prevalencia de diabetes (DM) tipo 1 era del 4,3% y de DM tipo 1121,6%. En el momento de la inclusión el 16,7% presentaban enfermedad coronaria, 13,9% insuficiencia cardiaca, 11,6% arritmias, 2,0% ACVA y 5,5% enfermedad arterial periférica. El índice de comorbilidad de Charlson era de 6,53_2,3. El 75,8% de pacientes eran hipertensos (74,4% en tratamiento farmacológico, 40% mal controlado). El 34,1% presentaba dislipemia. Un 83,2% de los dislipémicos no tratados y un 52,7% de los considerados no dislipémicos cumplían criterios para precisar tratamiento. El 11% era fumador y el 26,6% exfumadores. El 47,4% presentaba un peso superior al adecuado. El 22,2 % de los enfermos presentaba PTH > 300 pg/dl. El 68,8% tenía una hemoglobina > 11 g/dl, un 89,4% ferritina > 100 ng/ml y un 66,5% un IST > 20%. En resumen, estamos aún lejos de cumplir los objetivos de las guías de riesgo CV, pero conocemos con más precisión estos parámetros y hemos identificado oportunidades terapéuticas para mejorar la evolución y el pronóstico de nuestros pacientes.

Palabras clave: Riesgo Cardiovascular. Hemodiálisis. Anemia. Guías de tratamiento. Hipertensión. Lípidos.

INTRODUCTION

Hemodialysis (HD) mortality has not been significantly reduced in recent years in spite of technical dialysis advancements.[1,2] This is due, in part, to the steadily increase of incident patients' age and comorbidities. Data from other countries show a high prevalence of classical cardiovascular (CV) risk factors (RF) such as hypertension (AHT), ventricular hypertrophy (LVH), diabetes, dyslipemia, or previous CV events.[3] Other renal failure (CRF)-related RF such as anemia, hyperhomocysteinemia, chronic inflammatory state, oxidative stress, or hyperparathyroidism are specially linked to CRF. CRF itself worsens CV prognosis[4,5] and, thus, it is included as an independent RF in JNC VII update.[6] On the other hand, the presence of CV pathology accelerates progression to CRF.[7] This kidney-heart relationship is closer everyday, thus considering the kidney as a basic part of the CV system, with the same agents for damage and progression, and with similar prognostic factors and prevention strategies.[8] In spite of this, several studies point out an underuse of medications that have shown to improve CV prognosis in the general population.[9] For all these reasons, it is not surprising that almost half of the deaths in HD have a CV origin.[2,10]

The magnitude of this problem in HD has lead to the establishment of expert committees that try to alert nephrologists about CV risk[8] and propose management guidelines.[11] The appropriate approach should be started at early CRF phases by establis-

hing an individualized RF profile on which making a plan.[8,11] Thus, we today have clinical guidelines for managing CV risk,[11] hyperlipidemia,[12] AHT,[13] osteodystrophy,[14,15] and anemia,[16] among others. However, many of these guidelines are based upon data from north American studies that should not be extrapolated to our country, and in them, there is the recognition of the scant data on which some recommendations lie.[12] On the other hand, guidelines publication does not mean their acceptance and fulfillment. For example, with anemia, seven years after the first guidelines were published the goal of 85% of the population with hemoglobin (Hb) > 11 mg/dL is not accomplished, although a steady improvement of the results has been demonstrated.[17] For other CV risk factors, the information level is clearly insufficient.

Here we present the descriptive analysis of cardiovascular risk in the population included in the MAR study, fulfilling this way one of the secondary goals of this study.

MATERIAL AND METHODS

Study design

This is a prospective, descriptive, multicenter, open study of case series. Its main goal is to assess global morbimortality, especially of cardiovascular origin, and their relationship with the degree of anemia. Secondary objectives are the description of usual management patterns of these patients and reached control goals.

The study is based on a representative sample of CRF patients from any etiology, submitted to dialysis. The reference population is made of prevalent patients on HD, 18 years and older, that had initiated their treatment during January 1999-march 2001, and that had not received a previous renal transplantation. Treatment period lasted 4 months (march 2001-july 2001), and a 24-months follow-up period was initially programmed. It was advised to implement the recommendations of the «European Therapeutic Guidelines for optimal management of anemia in chronic renal failure»,[16] although patients may, or may not, be on EPO treatment according to authorized conditions of use.

A two phases conglomerate sampling was performed, the department being the first sampling phase and the patient on hemodialysis the second sampling phase. One hundred and nineteen centers (65 hospitals and 54 dialysis centers) have been included, stratified by number of patients in order to obtain a auto-weighed sampling allocation between 10 and 20 patients per center. Sample size was estimated from the prevalence and mortality data of the 1998 Registry, with a growing projection based on historical data. The final sample included 1710 cases (929 hospital patients and 781 dialysis center patients), with a ± 0.03 estimated sampling error and a 95% confidence interval.

Information gathering was done by doctors on a specific logbook (DRLB). This DRLB included vital statistics and particulars: gender, age at inclusion, transplantation candidate, working status, main CRF cause and date of diagnosis, concurrent pathologies, as well as treatment parameters and outcomes with dialysis regimens, anemia, and modifiable CV risk factors.

Follow-up check-ups were done at 1 and 3 months, and every 3 months thereafter, until the end of the study. Check-ups included clinical data, dialysis parameters (kT/V daugirdas, nPCR, and TAC Urea);[22] biological parameters; anemia management protocol; antihypertensive drugs; and hyperlipidemia, as well as events (cardiovascular and non-cardiovascular), hospital admissions, renal transplantation, and death, whenever they occurred.

The presence of concomitant pathologies with a prognostic effect on mortality, based on the Charlson's comorbidity index, was recorded as an added comorbidity datum. This index is compounded by 19 comorbid conditions that have an specific load and includes age. It is a simple method to adjust comorbidity in patients included in prospective studies and it has been validated for patients with end-stage renal failure.[19]

To assess the accomplishment of clinical and therapeutic goals, the following guidelines were selected: the NFK K-DOQI Guideline for dyslipemia management,[12] applying the secondary prevention objectives of the «Third Report of the National Cholesterol Education Program (NCEP) -HDL > 40, LDL < 100, triglycerides < 180;[21] K-DOQI guidelines on dialysis parameters;[22,23] K-DOQI guidelines on hyperparathyroidism management[15] and arterial hypertension management goals according to recommendations of the EDTA guidelines for predialysis values (140/90).[11]

Statistical analysis

Outcome analysis has been eminently descriptive according to the study goals. In the statistical analysis, the first step was to calculate estimates corresponding to each one of the variables included in the study, expresses as percentages or position parameters (mean, median), and scattering parameters (stan-

Table I. Comorbid factors prevalence at the beginning of MAR study

	Total	MAR Diabetics	NO DM	Spanish collab.	DOPPS	US registry	CHOICE
Age	64.4	*66.2	63.7	61.2	60.1	61.0	57.8
AHT	75.8%	*82.1%	73.7%	66.4%	84.70%	78.40%	74.0%
Coronary dis.	16.7%	*20.8%	15.3%	25.4%	47.90%	24.90%	21.0%
Arrhythmia	11.6%	12.4%	11.3%	11.9%	SI)	6%	5.0%
Cardiac failure	13.9%	*20.55%	11.7%	15.1%	43.90%	31.50%	25.0%
ACVA/Cerebrovascular dis.	2.0% (ACVA)	*4.2%	1.1%	SI)	16.9% (E CB/V)	9.40%	8.0%
Peripheral arteriopth.	5.5%	*12.9%	2.9%	SD	24.10%	14.20%	13.0%
Hyperlipidemia	34.1%	*41.9%	31.4%	SI)	SI)	SI)	SI)
Obesity	14.0%	*21.4%	11.5%	SD	16.1%	SI)	SI)
Smoker/ Ex < 1 y.	14.0%	*10.6%	*15.1%	SD	SD	5%	8.0%
Ex smoker >1y.	23.6%	24.1%	23.4%	SI)	SD	SI)	SI)
Diabetes I /II	4.3% / 21.6%	-	-	6.0 /15.2 %	48.10%	44.6%	40.0%

Data obtained from the following studies in the literature are compared: Spanish Collaborative Study on Anemia,[42]DOPPS,[38]and American registry.[2] **NYHA Grade II or greater failure (13.5% in Dm vs. 5.9% in no DM; p < 0.001). * P < 0.005 in DM vs. no DM (student's t test and χ^2, according to variable), the remaining n.s. ACVA: acute cerebrovascular attack. Cerebrovascular dis., cerebrovascular disease. AHT, arterial hipertensión. DL: data lacking.

dard deviation, range), according to variables nature. Chi-squared test for categorical variables and Student's t test and Mann-Whitney U test for other situations were the used techniques for the described comparisons. The database and the analysis were performed with SPSS software (10.0 version, SPSS inc., Chicago, IL, USA).

Sample characterization

Finally, 1710 prevalent patients from 119 centers were included, with 15.9 ± 11.1 months on dialysis. This accounts for 18% of total incident patients between 1999 and 2000, and 8% of prevalent patients on HD at the end of the year 2000, according to the National Registry estimate.[1] 54.3% received hospital-based HD and the remaining did so in concerted centers, with a mean age of 64.4 ± 13.6 years (range 18-92) and 60% were males. Distribution by age intervals (according to the Spanish Registry intervals) was 10.3% (15-44); 31.3% (45-64); 36.4% (65-74); 22.0% (≥ 75 years). CRF etiology was: diabetes 22.3%; glomerular 15.8%; vascular 13%; interstitial 9.9%; polycystic 8.6%; unknown 21.8%; other causes 7.1%.

Charlson's comorbidity index was 6.53 ± 2.3, with an interval distribution of 30.7% for values ≤ 5, 36.9% fir values 6-7, and 32.4% for values ≥ 8. 36.7% of the patients were included in the renal transplantation waiting list (as an indirect comorbid index). 9.6% received conventional HD through a catheter, 80.3% through a native fistulae, and 10.1% through a prosthetic access (PTFE-Gore®). Patients received three sessions per week with a duration of 11.1 ± 1.3 h/week, and 39.8% used high permeability membranes (> 20 mL/min/h/mm Hg).

RESULTS

Initial cardiovascular comorbidity and hypertension management

At the time of inclusion, 75.8% of the patients were hypertensive, 16.7% had coronary heart disease, and 13.9% had different degrees of heart failure, 11.6% had heart arrhythmia, 2.0% ACVA, and 5.5% peripheral arterial disease. Conventional CV RF are shown in Table I for diabetic and non-diabetic patients, and are compared to available data from the USRDS Registry and from European data from DOPPS and ESAM studies. Of note, diabetic patients have greater comorbidity and their only present CV RF is cigarette smoking.

74.4% of hypertensive patients (56.4% of the total) were on antihypertensive drugs, with a mean of 1.65 drugs per patient. Of them, 31.6% were on ACE inhibitors, 19.5% on ARA-II, 55.95% on calcium channel blockers, 23.42% on β-blockers, 27.4% on vasodilators and 6.5% on diuretics. 14.4% received three or more drugs, 32.4% two drugs, and 53.2% only one drug. Systolic/diastolic blood pressure numbers were 139.7 ± 20.9 / 75.2 ± 10.9 mmHg pre-HD and 128.4 ± 20.2 / 71 ± 10.4 mmHg post-HD.

When analyzing fulfillment of valid European guidelines,[11] 59.9% of patients had a pre-dialysis SBP/DBP < 140/90 mmHg, whereas the remaining 40.1% were poorly controlled, because of isolated systolic AHT (35.1%) or increased DBP (5%). The percentage of well-controlled patients increased to 65.6% within one year of follow-up, with 31.3% of isolated systolic hypertension. At the end of follow-up, distribution of used drugs was very similar, except for diuretics that dropped to 3.1%.

AHT management was poorer in diabetic patients with a lower percentage of well controlled patients (50.5% vs. 64.8%, with higher numbers for isolated systolic AHT (45.7% vs 30.6%) and not controlled DBP (4.7% vs 3.9%; χ^2 $p < 0.001$). However, we did not find differences in blood pressure control between genders.

Dyslipemia and other classical modifiable CV RF

At the time of inclusion, investigators considered that 34.1% of patients were dyslipemic, 69.5% of which were on treatment and the remaining 30.5% (10.4% of the total) were considered as hyperlipidemia without pharmacological treatment. Tabla II shows data on mean values for basic lipid profile, and their distribution by risk intervals at the beginning and at one year. Of note, only 28.7% fulfill guidelines objectives for all parameters simultaneously.[12] Of patients considered dyslipemic without anti-lipidemic treatment, total cholesterol was > 200 mg/dL in 37.3%; No-HDL Cholesterol > 130 mg/dL in 78.6%; LDL > 100 mg/dL in 95.2%; HDL < 40 mg/dL in 40.2% and triglycerides > 200 mg/dL in 21.5%. 83.2% of non-treated dyslipemic patients and 52.7% of those considered non-dyslipemic meet the criteria for treatment need according to the new NFK-K/DOQI guidelines.[12]

Diabetic patients have a poorer triglycerides control than the remaining patients, with 26.2% with a value > 200 mg/dL and 1.9% > 500 mg/dL versus 18.1% and 0.9%, respectively in the remaining patients (χ^2 $p < 0.01$). However, there were no significant differences in total cholesterol and cholesterol fractions.

11% admitted to be active smokers, 3% ex-smokers for less than one year, and 23.6% ex-smokers for longer than a year. Gender distribution shows significant differences (male/female; χ^2 $p < 0.001$) with regards to cigarette smoking: smokers, 15.6% vs 4.6%; ex-smokers for less than 1 year, 4.9% vs 0%; ex-smokers for longer than 1 year, 38% vs 1.5%. 18.5% of smokers and ex-smokers had COPD versus 4.6% in never smokers, and only 24.1% of COPD patients had never smoked. At the end of the follow-up period, smokers rate had decreased to 9.0%, increasing the ex-smokers rate.

Table II. Lipid profile in patients in MAR study

NCEP III recommendations	MAR		CHOICE	
	Baseline	Final	With hypolipemics	Without (84%)
Total cholesterol (mg/dL)	177.9 ± 38.3	174.2 ± 40.3	201 ± 4.1	186 ± 1.7
< 200 optimal	73.2	76.6	57	65
200-239 upper limit	20.8	17.5	20	23
≥ 240 high 6.0	5.8	23	12	
Triglycerides (mg/dL)	156.5 ± 101.1	147.7 ± 82.5	250 ± 14	189 ± 5
< 100 optimal	58.7	62.5	SD	SD
151-199 upper limit	19.8	18.2	SD	SD
≥ 200 high 20.4	19.3	52 ± 4.4	34 ± 1.7	
• LDL (mg/dl)103.6 ± 31.5	100.2 ± 34.7	111 ± 4.1	106 ± 1.5	
< 100 optimal	44.1	51.8	SD	SD
100-129 suboptimal	36.0	29.4	SD	SD
130-159 upper limit	14.8	13.3	SD	SD
≥ 160 high 5.1	5.5	14 ± 3.2	8.3 ± 1.1	
• HDL (mg/dL)44.5 ± 18.2	45.8 ± 15.6	43 ± 1.4	43 ± 0.6	
< 40	40.6	37.4	48 ± 4.4	45 ± 1.8
40-59	49.1	47.9		
≥ 60	10.3	14.7	SD	SD

Mean values and ranges are shown, with classification by intervals. The proposed goals proposed by the European guidelines are shown, with are in agreement with those from NECP for secondary prevention and with the CHOICE study results.[3]

Body mass index distribution (BMI: criteria of the European Endocrinology Society) was: 3.6% had low weight; 48.3% appropriate weight; 17.9% grade I overweight; 16.3% grade II overweight; 11.1% grade I obesity; 2.4% grade II obesity; and 0.5% grade III obesity. Patients with low weight have a lower albumin (36.2 ± 3.8 vs 38.3 ± 4.2, Student's t test, $p < 0.01$). Finally, 74% of women were postmenopausal.

CV RF specific to dialysis patients: anemia, hyperparathyroidism, and others

A detailed description of anemia management is not the aim of the present analysis and, thus, we will only highlight the most relevant data as another CV RF. At the time of inclusion, mean Hb was 11.7 ± 1.5 mg/dL, and 8% of patients had required at least one blood transfusion within the previous 4 months. 28.7% start EPO treatment 8.5 ± 9.6 months before HD onset, 42.7% simultaneously with HD, and 28.6% afterwards. At the beginning of HD, mean Hb was 9.7 ± 1.6 mg/dL and 81.4% of patients had a Hb level < 11 mg/dL. When analyzing fulfillment of EBPG[16] and DOQI[20] guidelines goals at inclusion, we find that 68.8% have an Hb level > 11 mg/dL, 89.4% a ferritin level > 100 mg/mL, 66.5% an IST > 20%, and 61.1% met all these criteria. Patients that exceeded both ferrokinetics goals had a better control of their anemia (30.7% vs. 35.8% Hb > 11 mg/dL; χ^2 $p < 0.05$).

At inclusion, the percentage of patients that did not reach the recommended values for urea kinetics (Kt/V daugirdas > 1.3, nPCR < 1 mg/kg/day, and TAC > 45 mg/dL) was 36.8%, 33.9%, and 38.9% respectively improving at one year with 10.1%, 30.9%, and 29.8%, respectively (χ^2 $p < 0.001$).

The most relevant nutrition parameters are: 3.6% of patients had low weight; mean nPCR 1.16 ± 0.36 g/kg/day, and mean albumin 37.5 ± 5 g/L, with a distribution of 19.66% < 35 g/L, 55.1% 35-40 g/L, and 25.2% > 40 g/L.

Mean PTH value was 208.1 ± 20.6.1 pg/dL, with a distribution of 19.8% with PTH < 50 pg/dL, 31.9% 51-150 pg/dL, 26.1% 151-300 pg/dL, 10.8% 301-450 pg/dL, and 11.4% > 450 pg/dL. Thus, at the beginning 22.2% of patients and at the end 23.3% were above the current recommended ranges[15].

DISCUSSION

Design justification and sample significance

The MAR study is the first multicenter prospective study performed with the main goal of analyzing the relationship between anemia and morbimortality, and with secondary objectives of describing these events as well as the clinical management patterns and target results in our patients[17].

The inclusion of prevalent patients with a mean time on HD lower than 16 months, and in any case lower than two years, has allowed us to shorten the recruitment period and facilitate the intermediate-term follow-up. This design may undervalue the prevalence and effect of RF since patients with the highest risk tend to die soon (survival error), but it also excludes patients transplanted within the first treatment months, generally with less comorbidities.

Sample size was calculated to be 1500 patients, a clearly outnumbered figure, including 15% more patients that started on HD between 1999 and 2000, with more than 8% prevalent patients by the end of the year 2000. Comparing with the data from the last registry,[1] we find a similar distribution by age intervals and CRF etiology, and a percentage of patients in waiting list for transplantation similar to that notified by the ONT (National Organization for Transplantation).[24] It is not surprising since 119 centers have participated from all over the country and with auto-weighed random sampling. Anyhow, conclusions drawn from this study have to be considered according to its design. Of note is the steady increase of diabetic nephropathy, which in the National Registry is increased from 17.5% in 2000 to 21.5% in 2001,[1] a percentage similar to the one in our study but that is still well below of the north American 44% prevalence.[2] For all these reasons, we consider that the MAR study represents the population currently on HD in our country, and makes a difference with the USRDS registry.[2] Indeed, our population is slightly older, with a different race distribution, a similar distribution by gender, a lower diabetes prevalence, and a different comorbidity profile (table I).

CV risk factors and comorbidity

Patients in the MAR study present high morbidity and CV risk, something foreseeable since 42% of HD mortality has a CV origin.[1] The CHOICE study has demonstrated a higher prevalence of classical CV RF in HD than the one in NAHNESIII study, even after adjusting for age, race, gender, and existence of previous events.[3] On the other hand, CV comorbidity is associated to accelerated progression to ESCRF and, finally, CRF itself has shown to be a CV RF[5] that is included as such in the recent JNC III update.[6] It seems clear that CV disease and CRF share triggers and progression factors and are frequently

associated in an individual patient. This has led to the new integrating paradigm of the cardio-renal syndrome.[25] For example, if the risk of suffering a de novo AMI with 10 years on HD is 20%, we must consider this type of patients in the same risk group as those with a previous AMI and normal RF.[26] For that reason, and even lacking specific studies in HD, north American and European consensus recommend an individualized «risk reduction» policy with the strict objectives of secondary prevention for heart diseased people.[25-27] This lack of information is more relevant in our setting. The present work brings data that may me useful as an initial reference about the prevalence of certain events and CV RF in a large sample from the prevalent HD population.

Intervention on classical RF such as AHT, obesity, hyperlipidemia, and cigarette smoking has reduced the risk in the general population. However, systematic action on CV RF in HD is surprisingly low, less than 50% of patients with coronary heart disease in HD receive medications that have shown to reduce mortality in the general population.[9] Perhaps, this is the reason why this effect has not been demonstrated in HD.[9]

AHT is an independent RF for de novo congestive heart failure (CHF),[28] myocardial ischemia,[29] LVH development,[30,31] and mortality,[32,33]in HD. Appropriate management of blood pressure reduces the risk in these patients, so that a pre-dialysis blood pressure less than 140/90 is recommended.[11] However, publication of guidelines does not mean their fulfillment. The CONTROLPRESS study, done in our country on more than 7000 hypertensive patients without CRF, shows that only 28.8% of the population is properly managed, and that 67.8% have and SBP > 140 and 39.6% a DBP > 90[34,35]. More importantly, in 88% of the cases the physician does not change treatment in the follow-up visit of a patient with BP out of range. Patients included in the MAR study are assessed every 48 h by health care staff, they receive medication and they are submitted to advanced techniques. However, 4 out of 10 still are out of control, similarly to other studies,[36] and only 5% improve within one year of follow-up. The results would be worse by using the goals recently proposed by the JNC VII for and elderly population with ESCRF and with more than a fourth of diabetics.[6] The role of systolic AHT as a mortality RF in the general population[6,37] and in HD[33,36] is especially relevant in the elderly. Previous studies in our country recommend a strict control of water balance and prolonged HD sessions to improve BP control[35]. We should not forget the hypotension-associated risk in HD, for these patients need to be closely monitored.[3,33]

Dyslipemia prevalence in HD varies depending on criteria used, being up to 90% in some series.[27] The most usual lipid profile in HD includes normal or elevated total cholesterol, LDL slightly increased, low HDL, and high triglycerides.[12] Current guidelines recommend the use of statins if there is no response to diet, with LDL between 100 and 130 mg/dL, or from the beginning if there is an associated previous CV event and/or if LDL is greater than 130.[12] It is recommended to separately use statins and gemfibrozil for cholesterol or triglycerides control, respectively, together with bimonthly follow-up of liver enzymes and lipid profile because of the risk of collateral effects[23]. The treatment goals applicable to these patients are the same as the NECP III for the secondary prevention in the general population and are shown in Table II. In our study, 30% of patients diagnosed with hyperlipidemia do not receive specific treatment and only 35.3% meet all the lipid profile goals. Although the data have been gathered before the publication of the last NKF-K/DOQI guidelines, our goal assessment identifies an important opportunity for therapeutic improvement. In fact, more than 80% of non-treated dyslipemic patients would need pharmacological treatment according to these new criteria[12].

Obesity is generally associated to sedentariness and dyslipemia, and promotes a rapid progression to vascular disease in the general population. However, the effect has not been confirmed in HD patients[38]. In the DOPPS study, overweighed patients present a higher survival rate, especially in the subgroup that accumulated more comorbidities and risk for other factors. According to the authors, overweight might avoid hyponutrition and select for a better prognosis, or it might be without an effect before the accumulation of other proatherogenic factors.[38] In this line, the CHOICE study finds a BMI and an obesity prevalence lower than that in the general population[3]. Anyhow, the group of patients with obesity range from I to III is out of the advisable range. Another group that needs special attention is the one with low weight because of associated hyponutrition. Although this is not a specific study on nutrition, we find out theses patients had a lower albumin. Albumin works as a hyponutrition marker, and of inflammation. The contribution of cigarette smoking to mortality, CV risk and to CRF progression justifies its withdrawal. This goal was achieved in 3 out of 14 smokers during their last follow-up year at the nephrology department, and in 23.6% in previous phases. However, the rate of active smokers is lower than that in the general population and in other studies in HD[3] that notify 15% of smokers and 61% of smokers and/or ex-smokers. It may be that this fact

is due to the influence of CV risk on the decision to quit smoking.

The chance of having an AMI in a patient that has already had an AMI is multiplied by four in HD.[9] The presence of previous cardiovascular events in our setting is very high and points out, in the one hand, missed opportunities for therapeutic control and, on the other hand, the group with the greatest risk. In comparison with registries from other countries, such as USRDS, we have lower heart failure, coronary disease, and peripheral vascular disease prevalences, with a greater arrhythmia incidence.[2,39]

Diabetes prevalence among patients with grade 5 CKD keeps on increasing and has gone from a 29.2 per million population to 107 pmp/year in 10 years, in the USA.[13] The 5-year mortality rate among diabetics is 65%, more than twice for non-diabetics (30%)[13]. Diabetic patients from the MAR study are older and have more associated comorbidities and CV RF. We have found a higher AHT and dyslipemia prevalence among diabetics, with a poorer control of these CV RF. They also show a higher obesity and peripheral, cerebral and coronary arteriopathy incidence, as well as heart failure. On the other hand, proper glycemic control has shown to reduce mortality in these patients as well as CRF progression and eventual dialysis.[13] Although we do not have data on glycemic control in our study, we should remind that the goals for ESRD are less stringent than in early nephropathy phases, setting up glycosilated Hb at around 7.5-8%[13].

LVH is at the same time a consequence of hypertensive and renal disease and an independent mortality risk factor. It has been demonstrated that both in advanced CRF and in HD development of LVH is related to AHT and anemia.[13] We have preliminary evidence that anemia and BP control promotes LVH regression, both in HD and in advanced CRF.[32,40] Recently, it has been shown that patients whose LVH subsides after BP and anemia control have a better prognosis that those without control. The MAR study does not include ecocardiographic parameters, but it does include data on anemia and BP control, so that we hope to find a relationship between appropriate management of these parameters and CV morbimortality.

Consideration of anemia as a CV RF pertaining to CRF is substantiated by previously demonstrated data such as: the pathophysiological relationship between anemia and LVH and coronary ischemia, the role in LVH progression in clinical and experimental studies, ventricular damage reversibility when correcting anemia, and lastly, the association between retrospective clinical trials with cardiovascular morbimortality. Very recent data from the European DOPPS study have strengthen the role of anemia as a risk marker by establishing, in a prospective study, the association between anemia and morbimortality.[41] On the other hand, there exist preliminary data on the association between anemia control and lipid profile improvement, which may contribute to its cardiovascular benefits[39]. Our data are comparatively better than those from previous studies in our country[42], but the goals proposed more than 6 years ago have not been reached yet[42].

Hyperparathyroidism has been proposed as a specific CV RF in uremia by means of several pathophysiological mechanisms such as calcifications, proatherogenic effect, and increase in myocardial calcium levels.[43] Some clinical studies demonstrate an association between phosphorus and PTH levels and Ca × P product on the one hand and CV complications on the other hand; and vascular calcifications are an increasing epidemic.[43,15] In order to carry out a detailed analysis it would be necessary to know other data such as medical and surgical treatments, calcium and phosphorus levels, concentration in the HD bath, and other elements that would need a study with that specific goal. Even so, we would like to highlight that almost one fourth of patients is above the 150-300 pg/dL DOQI guidelines recommended range,[15] even if dealing with a prospective prevalent cohort with a mean duration on HD longer than one year. More is to say, control does not improve within one year of follow-up. Values below 150 pg/dL may be inappropriate but additional information, such as osteodystrophy type or existence of previous parathyroidectomy, is required for its assessment.

Current guidelines establish minimum values for urea kinetics, based upon its relationship with patient's survival[22] and, thus, we have included them as co-variables. However, dialysis adequacy requires other issues such as ultrafiltration control, pre- and postdialysis BP control, and daily and individualized follow-up of the patient. In fact, a correlation between time spent by the nephrologist and better clinical course has been demonstrated.[44] A proportion of our population does not reach the goals for urea kinetics, and even so there is a resistance to increase time of sessions (only 54.2% exceed 4 hours), which is compensated by a high usage rate of special membranes. Interdialysis weight gaining has been associated to a poor BP control and heart overload, so that it has been recommended to maintain an interdialysis weight gain lower than 5%. In our study, more than 10% of the patients exceed those limits and present a poorer BP control. A longer dialysis time might favor and proper BP and phosphorus control and contribute to reduce CV risk.

CONCLUSIONS

This analysis has allowed us to know in detail what is the usual practice in multiple issues regarding patients' management. It also establishes clear differences with north American registries regarding patients' profile, vascular access management, dialysis, anemia and comorbidity. A high prevalence of cardiovascular problems is confirmed in our HD patients, especially among diabetics. We are still far from fulfilling guidelines' goals for CV risk, but we more accurately know these parameters and we have identified therapeutic opportunities to improve progression and prognosis in our patients. Among them, we might highlight a better lipid profile control, dialysis efficacy, blood pressure control, and anemia management.

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