

Microalbuminuria in hypertensive patients: Evaluation of one-year treatment with irbesartan

FERNANDO DE ÁLVARO, OLGA VELASCO, JESÚS HONORATO, CARLOS CALVO, INMA PARRONDO, ON BEHALF OF KORAL HT INVESTIGATORS

Hospital Universitario La Paz, Madrid, Spain; Scientific Department, BMS, Madrid, Spain; Clínica Universitaria de Navarra, Pamplona, Spain; and Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain

Microalbuminuria in hypertensive patients: Evaluation of one-year treatment with irbesartan.

Background. Microalbuminuria is an important cardiovascular risk factor, and appears to be a marker of early arterial disease in patients with and without diabetes and/or hypertension. The aim of this study was to investigate prevalence of albuminuria in hypertensive patients in clinical settings, as well as to assess the efficacy of the angiotensin receptor blocker irbesartan on the evolution of this risk marker in habitual clinical practice.

Methods. KORAL-HT is a prospective, multicenter 1-year follow-up study in inadequately controlled hypertensive patients. Demographic data, major cardiovascular risk factors, albuminuria, and clinical parameters were recorded at baseline and at 6-month and 12-month visits. During the year of follow-up, the patients received antihypertensive therapy with irbesartan in addition to their usual antihypertensive regimen.

Results. A total of 1657 [802 diabetics (48.4%) and 855 nondiabetics (51.6%)] hypertensive patients were studied. The prevalence of microalbuminuria in this sample was 62.5%. After 1-year treatment with irbesartan, the percentage of patients with normoalbuminuria grew from 17.1% at baseline to 40.9% at 1-year follow-up. Blood pressure (BP) decreased from $157.3 \pm 13.7/93.6 \pm 9.2$ mm Hg at baseline to 139.8 ± 13.12 mm Hg and $136.1 \pm 11.6/80.1 \pm 8$ mmHg at 6- and 12-month visits, respectively. The percentage of patients who achieved BP targets increased progressively, 57.2% at 6 months, and 70.1% at the study end.

Conclusion. This study shows that the population attending Spanish HT centers have high prevalence of microalbuminuria. The addition of irbesartan to the usual treatment in poorly controlled hypertensive patients significantly improved BP control, and reduced microalbuminuria both in diabetic and nondiabetic patients. Our study confirms that similar results can be obtained in normal clinical practice as in controlled clinical trials.

Cardiovascular diseases are the primary cause of death and disability, and as such, require the development of strategies for diagnosis, prevention, and treatment. Urinary albumin excretion (UAE) in hypertensive patients

is a continuous and progressive marker of renal damage and cardiovascular events. This technique can be carried out cheaply and easily [1, 2]. Target organ damage is more frequent in patients with microalbuminuria [3], and these patients have a higher rate of left ventricular mass (LVM). High albumin/creatinine ratios correlated with an increase of morbidity and mortality in hypertensive patients and in patients with left ventricular hypertrophy [4], as well. The relationship between microalbuminuria and other risk factors has been widely demonstrated [5]. Microalbuminuria reflects vascular damage, and appears to be a marker of early arterial disease. For this reason, the assessment of urinary albumin excretion is an important aspect for risk factor stratification in hypertensive patients.

Blockade of the renin-angiotensin system (RAS) inhibits the vasoconstrictive effect of angiotensin II on the renal efferent glomerular arteriole. The mesangial cell proliferation induced by angiotensin II is also reduced. This type of action has a highly significant renoprotective effect, important in hypertensive patients, particularly in diabetics [6–7].

The European Society of Hypertension and Cardiology and the Seventh Report of the American Joint National Committee guidelines recommend the monitoring of urinary albumin excretion (UAE) and RAS intervention in hypertensive patients and, even more strongly, encourage such monitoring and intervention when there is evidence of renal damage, and in diabetic patients [8–9].

The PRIME study showed that irbesartan treatment significantly modified the progression of renal damage in hypertensive patients with type 2 diabetes mellitus with microalbuminuria or proteinuria [10–11]. However, there are insufficient data available on the prevalence of albuminuria and the efficacy of RAS blockade in the reduction of urinary albumin excretion in hypertensive patients followed in clinical practice conditions. Therefore, the objective of this study was to estimate the prevalence of microalbuminuria/albuminuria in poorly controlled patients attending hypertensive units in Spain,

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and to evaluate the effect of 1 year's treatment with irbesartan on microalbuminuria/albuminuria in hypertensive patients in conditions of clinical practice. The secondary objectives were: (1) to evaluate the changes in systolic and diastolic blood pressure (SBP and DBP) caused by the irbesartan treatment; (2) to assess the percentage of patients who achieve target blood pressure (BP); and (3) to determine the effect of treatment with irbesartan on the evolution of renal function.

DESIGN

KORAL-HT is an observational, prospective, 1-year follow-up study in hypertensive, uncontrolled patients, to whom irbesartan was added to their antihypertensive treatment. Measurements were made at baseline and at 6- and 12-months' follow-up. The protocol was approved by the Clinical Research Ethics Committees.

METHODS

The study was carried out by 125 investigators from 105 hypertension units in Spain. A total of 1657 uncontrolled hypertensive patients (BP > 140/90 mm Hg in nondiabetics and BP > 130/85 mm Hg in diabetic patients) were studied and followed for 12 months. The patients who had been treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (ARBs) during at least the 2 weeks prior to inclusion were excluded. Patients with secondary hypertension or BP \geq 210/110 mm Hg, unstable hypertension, type 1 diabetes, hyperkalemia >5.5 mEq/L, contraindications for treatment with ARBs, or any serious concomitant disease which could affect follow-up were also excluded. BP determination was carried out according to the WHO guidelines [12]. Demographic data, major cardiovascular risk factors, associated cardiovascular disease, albuminuria, and clinical parameters were all recorded. Patients' visits were scheduled at the beginning, at 6 months, and at the end of the study (12 months).

Routine biochemical and microalbuminuria tests were performed by the laboratory of each center involved in the study, following the usual practice of the center. Based on the significance of the MICROHOPE study [2], which established that any level of microalbuminuria (A/Cr > 0.2 mg/mmol) directly correlates with cardiovascular morbidity and mortality, the inclusion of patients with microalbuminuria below 30 mg/day was permitted. All patients determined to have microalbuminuria who matched the inclusion criteria were admitted for a 1-year follow-up treatment with irbesartan. Renal function was evaluated with the Cockcroft-Gault formula.

The irbesartan regimen dose was titrated from 150 mg to 300 mg, and if target BP was not achieved, (BP < 140/90 mm Hg in nondiabetics, BP < 130/80 mm Hg in diabetics),

the following scheme of treatment was followed according to the physician criteria: (1) irbesartan 300 mg + hydrochlorothiazide (HTZ) 12.5 mg; (2) irbesartan 300 mg + HTZ 12.5 mg + other antihypertensive drug other than ARBs or ACEIs, until the patients reach the BP targets.

Statistical analysis

Data are expressed as mean \pm SD. Microalbuminuria levels are expressed as mean \pm SE. Student *t* test was used for baseline group comparisons, and Student paired *t* test was used when comparing the variables before and after intervention. Analysis of variance (ANOVA) was used for comparisons for >2 groups. General linear model was used to correct for confounding factors. Differences were considered statistically significant at $P < 0.05$. All calculations were performed using the software SPSS 11.5 for Windows (Chicago, IL, USA).

RESULTS

A total of 1657 patients were included in the study; 802 were diabetics (48.4%) and 855 were nondiabetics (51.6%). Mean systolic and diastolic BP at the time of inclusion was 157.7 ± 14.2 mm Hg and 93.3 ± 9.6 mm Hg, respectively. Pulse pressure (PP) was 64.4 ± 13.9 . Seventy-six percent of the patients were receiving previous pharmacologic antihypertensive treatment, while 23.65% were not. The previous antihypertensive treatment received was: calcium channel blockers (48%), diuretics (38.8%), beta-blockers (21.8%), alpha-blockers (13.6%), and other hypertensive drugs (3.8%). Among patients with previous hypertensive treatment, 79% were on monotherapy, 17% were receiving 2 antihypertensive drugs, 3.6% were receiving 3 drugs, and only 0.6% was receiving 4 or more antihypertensive drugs. Thirty-five percent of the patients were receiving lipid-lowering agents, and 20.5% were on antiplatelet therapy. Among diabetic patients, 70.6% were receiving either oral antidiabetic agents or insulin (78.6% of them were receiving oral agents and 24.4% received insulin). Mean (\pm SD) hemoglobin A_{1C} of the diabetic patients was $6.9 (\pm 1.4)$.

A percentage (17.1%) of the patients had an urinary albumin excretion in the range of normoalbuminuria, 62.5% microalbuminuria, and in 20.4% of the patients, the urinary albumin excretion was in the range of proteinuria. The mean 24-hour urinary albumin excretion rate was 317.8 mg/24 hours.

Table 1 shows demographic and clinical characteristics of the diabetic and nondiabetic patients at the time of inclusion in the study. Diabetic patients were older and heavier. Mean diastolic BP was lower, and mean pulse pressure higher in the diabetic patients. Ischemic heart disease, cerebrovascular disease, and peripheral artery disease were all significantly more prevalent among

Table 1. Baseline characteristics of the diabetic and nondiabetic patients

	Nondiabetics	Diabetics
N (Male/female)	855 (501/354)	802 (484/318)
Age ^a years (mean ± SD)	58.5 ± 12.7	62.3 ± 11
BMI ^a kg/m ² (mean ± SD)	28.7 ± 4.3	29.8 ± 4.6
SBP mm Hg (mean ± SD)	158 ± 14	157.4 ± 13
DBP ^a mm Hg (mean ± SD)	95.2 ± 10	91.2 ± 9
PP ^a mean ± SD	62.8 ± 13	66.1 ± 14
Target organ damage		
Ischemic heart disease ^a %	4.1	10.2
Cerebrovascular disease ^a %	2.1	5.9
Peripheral artery disease ^a %	2.8	8.4

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

^aP < 0.001.

Table 2. Biochemical data of the diabetic and nondiabetic patients at baseline (mean ± SD)

	Nondiabetics	Diabetics
Glucose ^a mg/dL	98.5 ± 14.5	156.8 ± 41.5
Creatinine mg/dL	1.1 ± 0.4	1.1 ± 0.3
Na mmol/L	140.4 ± 3.4	140.2 ± 3.9
K mmol/L	4.3 ± 0.4	4.5 ± 0.5
Uric acid mg/dL	6 ± 2.1	5.9 ± 1.6
Creatinine clearance mL/min	83.9 ± 34.5	79.7 ± 34.6
Total cholesterol mg/dL	217.6 ± 78.4	215.9 ± 41.5
LDL-C mg/dL	132.6 ± 35.8	131.6 ± 37.5
HDL-C mg/dL	51.5 ± 14.1	50.5 ± 14.8
Triglycerides ^a mg/dL	139.4 ± 82.2	165.8 ± 86.3
Albumin/creatinine ratio ^a mg/g	203.2 ± 114.7	328 ± 1725.9
24-h exc rate ^a mg/24h	276.2 ± 694.4	369.6 ± 686.9

Abbreviations are: Na, sodium; K, potassium; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; 24-h exc rate, 24-hr excretion rate.

^aP < 0.001.

diabetic patients (*P* < 0.001). Table 2 shows comparison of biochemical data at baseline between diabetic and nondiabetic individuals. Fasting plasma glucose and triglyceride concentrations were significantly higher in the diabetic patients (*P* < 0.001). Additionally, urinary albumin excretion (UAE) rate was significantly higher in the diabetic group.

Of the 1657 patients who started the study, 1151 completed the treatment follow-up according to the planned schedule. Given the conditions of normal clinical practice under which the study was performed, a dropout rate of about 30% was to be expected. The most common reasons for study withdrawal were: lost to follow-up for 392 patients; investigator’s decision in 10 patients; lack of compliance with protocol treatment or visit schedule for 9 patients; consent withdrawal for 6 patients; adverse reactions in 2 patients; and other reasons for 12 patients. The reasons for withdrawal were unknown for 75 patients. No significant differences (*P* < 0.01) were observed between the population that was included and that which was followed through to the end of the study, except for glycemia. Based on these results, we assumed that the

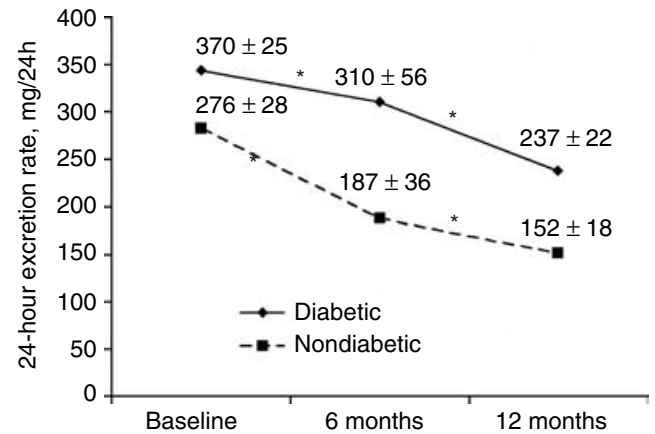


Fig. 1. Urine albumin excretion at baseline, 6-month, and 12-month visit in the diabetic and nondiabetic patients.

main characteristics of patients lost for the study follow-up would not modify the results.

During the study, the patients were treated with a mean dose of 250.7 ± 60.3 mg irbesartan. In the final visit, 76.3% of the patients were receiving treatment with 2 antihypertensive drugs, 18.3% were receiving 3 drugs, and 4.6% were receiving 4 or more antihypertensive drugs. Of the patients who received more than 1 drug, 29.4% received diuretics, 20% beta-blockers, 51% CCB, 20% alpha-blockers, and 2.9% other classes of drugs. In the initial visit, 32.9% of the patients were receiving antidiabetic treatment compared to the 15.3% at the final visit. The percentage of patients treated with lipid-lowering agents also fell from 33.5% in the initial visit to 20.6% in the final visit. There were no significant changes in antiplatelet therapy.

The effect of treatment on urine albumin excretion in diabetic and nondiabetic groups during the study period is shown in Figure 1. Mean 24-hour albumin excretion rate decreased significantly at the 6-month and 12-month follow-up measurements (*P* < 0.001). There was a significant and similar decrease in microalbuminuria in both groups.

The percentage of patients with normo-, micro-, and macroalbuminuria during the follow-up period is shown in Figure 2. The proportion of patients with urine albumin excretion in the range of “normoalbuminuria” grew significantly throughout the study, from 17.1% at the time of inclusion to 40.9% after 1 year of treatment (Fig. 2).

BP evolution during the study follow-up

Both systolic and diastolic BP, and also pulse pressure decreased significantly at the 6-month and 12-month visits. Blood pressure (BP) decreased from 157.3 ± 13.7/93.6 ± 9.2 mm Hg at baseline to 139.8 ± 13.1/82.6 ± 8.6 mm Hg and 136.1 ± 11.6/80.1 ± 8.1 mm Hg at 6- and 12-month visits, respectively. At the 6-month study

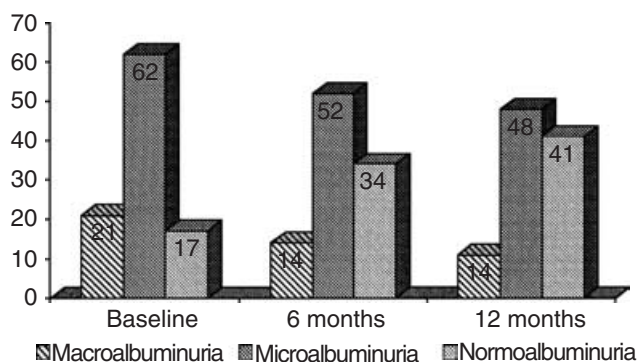


Fig. 2. Percentage of patients with macro-, micro-, and normoalbuminuria during the study period.

visit, 56.9% of the patients had achieved BP targets. After the 1-year treatment with the study protocol, 70.1% of the patients had achieved the study objective of BP. A higher proportion of nondiabetic patients achieved the BP target compared with diabetics (22%), but a lower BP objective was established for the diabetic patients.

Evolution of renal function in patients treated with irbesartan, based on the estimation of GFR using the Cockcroft-Gault equation

The mean GFR decreased from 81.9 ± 34 mL/min at baseline to 80.1 ± 31 mL/min at the end of the study ($P < 0.01$). However, when grouping the patients in diabetics and nondiabetics, the reduction is still significant in nondiabetic patients (83.9 ± 32 vs. 81.4 ± 30 , $P < 0.01$), but not in diabetic subjects (79.7 ± 37 vs. 79.8 ± 38).

There are other data worth mentioning, although not included in the study objectives. There was a significant reduction in fasting plasma glucose, which fell from a mean value of 124.8 ± 42.4 at baseline to 119.3 ± 35.4 after 1 year of treatment ($P < 0.001$). The reduction was more pronounced in the diabetic group. In addition, there was a reduction in total cholesterol (218.1 ± 71.3 vs. 203.3 ± 30.2 , $P < 0.001$), LDL cholesterol (132.5 ± 36.9 vs. 122.0 ± 29.5 , $P < 0.001$), and triglycerides (151.1 ± 81.8 vs. 143.4 ± 63.8 , $P < 0.001$). The reduction was more pronounced in the group of diabetic patients.

DISCUSSION

This study shows high urinary albumin excretion that was reduced by reaching BP targets with the addition of the ARB irbesartan in uncontrolled hypertensive patients attending hypertension units in Spain.

The objective of hypertension treatment includes the reduction of cardiovascular and cerebrovascular morbidity and mortality, and also, the reduction of the progression of renal insufficiency. Many studies in different

populations have shown microalbuminuria to be an important risk factor of cardiovascular morbidity and mortality, both in diabetic and nondiabetic patients. Determination of microalbuminuria should be a routine practice because its appearance, progression to proteinuria, or regression to normoalbuminuria are correlated with a higher or lower risk of coronary heart disease, stroke, or peripheral vascular disease. In other words, urinary albumin excretion is a marker of cardiovascular risk, and also a marker of treatment efficacy.

In the present study, we examined the prevalence of microalbuminuria in a sample of consecutive patients attending to the hypertension units of 15 hospitals included in the KORAL-HT study group, distributed throughout the country. In this nonselected sample of hypertensive patients, the prevalence of microalbuminuria was over 60%, much higher than the prevalence of 43% described in Spanish diabetics participating in the DEMAND study, and also higher than the 18% described in hypertensive patients attending primary care clinics in our country [13] and than the 11% for patients in the EPIC-Norfolk study [14]. This prevalence shows that patients seen in the hypertension units of the KORAL-HT study have a considerably higher cardiovascular risk. The higher prevalence of patients with microalbuminuria in our study can be accounted for by the higher presence of cardiovascular risk factors and target organ damage of our patient population, attended at specialized hospital-based hypertension units.

The patients included in the 1-year follow-up study (KORAL-HT) consisted mainly of an urban population, mean age 60.3 years, of which 48.4% were diabetics. The patients' age and risk factors imply a very high risk. Only 23.6% of the patients were not receiving antihypertensive treatment before their inclusion in the study. In general, diabetic patients were older, with a higher BMI and a higher prevalence of associated CV disease. The introduction and titration of irbesartan (150 mg to 300 to 300 + HCTZ) achieved a significant reduction in blood pressure throughout the follow-up period. A reduction of 22 mm Hg in SBP and 13.2 mm Hg in DBP was achieved compared to the baseline. The drop in blood pressure was maintained over the follow-up. The percentage of controlled patients was 56% at 6 months and 70% at the end of the study. The reduction in BP was remarkable, taking into account that most patients were already receiving other antihypertensive drugs. Mean blood pressure at the end of the study suggests that blood pressure control in clinical practice of patients with a high CV risk and/or diabetes can be similar to that obtained in controlled clinical trials [7, 10–11, 15]. The percentage of diabetic patients that achieved the blood pressure objective was less than in nondiabetics, reflecting a lower response to antihypertensive treatment in diabetics, which has also been seen in other studies.

Systemic BP reduction, and even more strongly, intraglomerular pressure drop, has been shown to effectively decrease the urinary albumin excretion rate. The present study was aimed at demonstrating the efficacy of irbesartan treatment to reduce microalbuminuria in uncontrolled hypertensive diabetics and nondiabetics in routine clinical practice.

Parallel to the significant blood pressure decrease, a remarkable reduction in the urinary albumin excretion rate was also observed. The proportion of patients with normoalbuminuria increased from 17.1% at baseline to 40.9% at the end of the study, while the percentage of patients with microalbuminuria dropped from 62.5% at baseline to 48.3% at the study end, and that of clinical proteinuria dropped from 20.4% at baseline to 10.7% at the end. Microalbuminuria decreased during the 12-month follow-up in spite of the absence of significant blood pressure changes in the last semester. There was a progressive reduction in microalbuminuria. At the end of the study, a global reduction in urinary albumin excretion rate greater than 60% was achieved compared to baseline, mimicking IRMA 2 study results.

Renal function was maintained rather stable over the study period (81.9 ± 34.1 baseline vs. 80.2 ± 31.6 $P < 0.01$ at study end). The reduction of GFR, minimal, was only significant in nondiabetic patients, and probably secondary to functional factors (reduction of BP and intraglomerular pressure induced by irbesartan treatment).

During the study there was an improvement in lipid parameters: reduction in total cholesterol and triglycerides with a significant rise in HDL cholesterol. Although our objectives did not encompass treatment and control of hyperlipidemia, investigators' intervention to correct lipid abnormalities was likely, albeit no changes in cholesterol lowering drug therapy were recorded. Besides, a possible beneficial effect of the renin-angiotensin system blockade on carbohydrate metabolism cannot be ruled out [17, 18].

CONCLUSION

High doses of irbesartan can reduce and even normalize microalbuminuria both in diabetic and nondiabetic patients.

The benefits achieved in BP control and microalbuminuria reproduce in the clinical practice the results obtained in controlled trials. The positive evolution of lipid and metabolic parameters support the benefits of observational studies, beyond the study primary end point.

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APPENDIX

Clinical investigators of the KORAL-HT study who provided and cared for study patients

Luis Miguel Lou Arnal, Ricardo Gómez Sánchez, Vicente Barrio Lucía, Francisco Martínez Deben, Michel Jaquet Herter, Alfonso Otero González, Ignacio Vazquez de Prada González, Ramón Pacheco Sarabia, Francisco Gil, M^a José Aladrén Regidor, Pedro Vives Aguéda, Julio Herrera Pérez de Villar, Francisco Fernández Vega, Salvador Tranche Iparraguirre, Joaquín Aracil Villar, Miguel Ángel Prieto Díaz, Ramón Delgado Lillo, José Enrique López Paz, M^a Jesús Domínguez Santana, Jesús Honorato, Francisco Martín Marín, Jesús Cebollada Muro, Najaty Suliman Jabary, José Bueno Gómez, José Vicente Lozano Vidal, Antonio Robles Iniesta, Pedro Escriche Roberto, Carmen Caro Narrillos, Jose M^a Martínez García, Emilio Marqués Contreras, Jose Antonio Madrigal Vilata, Fco Javier Martínez Martín, José Carlos Rodríguez Pérez, Saturnino Suárez Ortega, José Luis Gorriz Teruel, Jaume Planas, Francisco Javier del Cazo, Marc Cuixart Pérez, Josep Soler Amigó, Andrés de la Peña Fernández, Javier Tisaire Sánchez, Santos Casado Pérez, Juan Ocón Pujadas, Isabel Martínez Fernández, Agustín Minguez Sanz, Pedro Aranda Lara, Ana M^a Tormo Cantos, Alfonso Pérez García, M^a José Fernández-Rojas Luis, Rosa Sánchez Hernández, Carmen Mon, Jacinto Fernández Pardo, C. Pintor, Emilio López-Vidriero Abelló, Fco. Javier Rodríguez, Juan Antonio Divisón Garrote, Luis Miguel Artigao Roenas, M^a Eugenia Plagaro, José Javier Torrijos Gil, Jordi Calls Ginesta, José M^a Pascual, Pedro Cardona Ausina, Beatriz Acebrón Sánchez-Fortún, Juan Carlos Romero Pérez, Gabriel Pou Serradell, Carmen Rosa González Fernández, Carlota García Arias, Antonio Grilo Reina, Luis Miguel Ruilope, Antonio Liébana Cañivól, Josep Redon Ros, Blas Gil Extremera, Emilio Olivares García, Pedro Cipriano Gordo Fraile, Javier Vivanco Martínez, Ibrahim Aziz Basha, Dámaso Escribano Sevillano, Josep María Galcerán Gui, Ramón González, Javier Sobrino Martínez, Cesar González Martínez, M^a Concepción Laviades Álvarez, Rafael Virto Ruiz, Manuel Ángel Rodríguez Martínez, Fernando de Álvaro, Vicente Valor Font, Juanjo Villarreal Balza, Aquilino Sánchez Purificación, M^a del Mar Biechi Balda, Francisco Fernández Montero, Joaquín Franco Cebrián, Jose Latorre Hernández, Pilar Rosique Delmas, Pablo Gómez Fernández, Josep Bromsons, José Ramón Calabuig Alborch, Alberto Sanjuán Hernández, Lorenzo Pastor Mourón, Manuel López Jiménez, Adnan Hawari Meilud, Jesús Martín García, Joseph Esque Panavera, Carmen Suárez Fernández, Dámaso Sanz Guajardo, Diego Biedma Álvarez, José Luis Bianchi Llave, Francisco Pérez Corral, José Sabán Ruiz, Gonzalo de la Lama León, Antoni Pellegrí, Fco. Javier Guerediaga Madariaga, Julio Cesar Blázquez Encinar, Javier Solís Villa, M^a Cristina Ligorria Berguio, Benito Maceira Cruz, Rosario García Palacios, Esther Salces Sáez, Manuel Luque Otero, Melchor Rodríguez Gaspar, Jesús Grande Villoria, Fernando Tornero Molina, Ángel Sánchez Rodríguez, Celia Fernández-Torres, Jose Luís Asín Marcotequi, Juan José Zuzue Gaztelu, Gregorio Tiberio López.

Reprint requests to Fernando de Álvaro, Servicio de Nefrología, Hospital Universitario La Paz, Madrid, Spain.
E-mail: fdealvaro@infonegocio.com

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