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ORIGINALS

Albuminuria and cardiovascular risk: results of the KORAL-CARDIO study

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SUMMARY

Background and objectives: *Albuminuria is a marker of higher cardiovascular and renal risk in hypertension; it also indicates the need of a tighter control of blood pressure with drugs blocking the renin-angiotensin system. The objective of the* KORAL-CARDIO *study was to assess the clinical picture and management of patients with hypertension and cardiac disease and albuminuria not previously treated with angiotensin inhibitors.*

Methods: *A total of 2,711 hypertensive patients (44% female) with ischemic or hypertensive cardiopathy or atrial fibrillation and with a positive* screening *test for albuminuria was included. Type 2 diabetes was also present in 42%.*

Results: *Macroalbuminuria was present in 7.2% of non diabetic and 12.7% of diabetic patients, respectively. Associated complications were: 25% and 35% body mass index over 30 kg/m^2; 22% and 39% ischemic heart disease; 4% and 8% stroke; 19% and 22% atrial fibrillation; 42% and 53% high cholesterol levels; 8% and 8% grade 3 hypertension, for non-diabetics and diabetics respectively. Antihypertensive monotherapy was used in 66% of non-diabetics and in 63% of diabetics; only 7% of patients in both groups were treated with triple antihypertensive therapy.*

Conclusions: *Cardiovascular complications are very frequently associated to albuminuria in patients with hypertension and heart disease not previously treated with angiotensin inhibitors. Blood pressure control was clearly inadequate in this group.*

Key words: ***Hypertension. Cardiovascular diseases. Albuminuria.***

ALBUMINURIA Y RIESGO CARDIOVASCULAR. ESTUDIO KORAL-CARDIO

RESUMEN

Introducción y objetivos: *La presencia de albuminuria identifica a un grupo de hipertensos con mayor riesgo cardiovascular y renal y obliga a controlar mejor la presión arterial con fármacos que bloqueen el sistema renina-angiotensina. El ob-*

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jetivo del estudio KORAL-CARDIO *fue determinar las características clínicas y de manejo de pacientes con hipertensión, albuminuria y cardiopatía no tratados previamente con inhibidores angiotensínicos.*

Pacientes y métodos: *Se incluyen prospectivamente 2.711 pacientes (44% mujeres) de 64 años de media con hipertensión arterial, cardiopatía isquémica o hipertensiva o fibrilación auricular con positividad en la detección cualitativa de albuminuria. El 42% tenían además diabetes mellitus de tipo 2.*

Resultados: *El 7,2% de los no diabéticos y el 12,7% de los diabéticos tenían macroalbuminuria; el 25% y el 35% respectivamente tenían índice de masa corporal de más de 30 kg/m^2. Las complicaciones asociadas fueron: cardiopatía isquémica (22 y 39%), ictus (4 y 8%), fibrilación auricular (19 y 22%), hipercolesterolemia (42 y 53%), hipertensión de grado 3 (8% en ambos casos). Recibían tratamiento antihipertensivo monofármaco el 66% de los no diabéticos y el 63% de los diabéticos, y sólo el 7% triple terapia; otros tratamientos fueron: hipolipemiantes (41 y 57%) y antiagregantes (37 y 58% respectivamente).*

Conclusiones: *Las complicaciones asociadas a la albuminuria en hipertensos con cardiopatías, diabéticos y no diabéticos, no tratados con inhibidores angiotensínicos son muy frecuentes. El grado de control tensional fue escaso en este grupo.*

Palabras clave: ***Hipertensión arterial. Enfermedades cardiovasculares. Albuminuria.***

ABBREVIATIONS

ACEI = Angiotensin converting enzyme inhibitors
ARB = Angiotensin receptor blockers
CVD = Cardiovascular disease(s)
AHT = arterial hypertension
RAS = Renin-angiotensin system

INTRODUCTION

Clinical practice guidelines indicate that risk stratification represents one of the key elements to plan prevention and treatment strategies for cardiovascular diseases (CVD).[1-4] It is required to plan a global risk reduction strategy to prevent the clinical complications of arterial hypertension (AHT), dyslipidemia, and diabetes, in particular. In current guidelines, this risk may be estimated from demographical data, arterial blood pressure levels (particularly systolic BP), plasma lipids, and glycosilated hemoglobin. However, the same guidelines highlight that new markers of CVD severity should be included in this quantification that may also help as indicators of therapeutic efficacy.

One of these markers is albumin urinary excretion; its detection should be part of risk stratification of diabetic patients and patients with AHT since it has been demonstrated its close relationship with cardiac, vascular, and renal complications. Therefore, its reduction or reversion constitutes one of the main therapeutic goals in these patients.[1-5] The presence of albuminuria allows identifying a subgroup of subjects with more advanced disease, it represents a marker of organ damage, it enforces a stricter control of arterial blood pressure levels, and it orients on the need for using renin-angiotensin system (RAS) blocking drugs, which have been shown to be associated to greater cardiovascular and renal protection, especially in diabetic patients.[6-10] There are data suggesting that albuminuria is frequent among patients with CVD (in particular, coronary or hypertensive heart disease, and cerebrovascular disease) and that is accompanied by a worse prognosis,[11,12] but to date we lack large studies on the clinical characteristics of patients with albuminuria and CVD and on how they are treated in routine practice.

The aim of the *KORAL-CARDIO* study is to determine albuminuria degrees and associated clinical characteristics in a group of hypertensive patients with several heart diseases (atrial fibrillation, left ventricular hypertrophy, or chronic coronary heart disease) non-treated with RAS inhibitors, and to analyze the influence of type 2 diabetes mellitus on the outcomes.

PATIENTS AND METHODS

Study design

The *KORAL-CARDIO* study was designed as a multicenter, prospective, observational study. The recruitment period started on September of 2002 and

lasted 6 months; follow-up of each case is intended to be prolonged to 24 months. The present analysis makes reference only to baseline results, which will be presented separately for diabetics and non-diabetics.

Two hundred and fifty-nine cardiologists in charge of outpatient cardiology clinics participated in the study, and they were distributed throughout the entire Spanish territory. They consecutively included patients meeting the criteria specified below. The study was approved by the corresponding regulatory authorities (Spanish Drug Agency). All patients expressly consented to participate in the study after having been informed on its purpose and methodology.

Inclusion and exclusion criteria

All patients with arterial hypertension (arterial blood pressure ≥ 140/90 mmHg, treated or non-treated) and any of the following associated heart diseases were considered for inclusion: chronic or paroxysmal atrial fibrillation, left ventricular hypertrophy according to EKG criteria[5,13] or chronic coronary heart disease (angina, acute coronary syndrome with no previous ST segment elevation or previous revascularization) and having also albuminuria in quantitative determinations (see methods).

Excluded patients were those with: secondary arterial hypertension or with blood pressure levels > 210/110 mmHg, type 1 or unstable diabetes mellitus, heart failure, myocardial infarction with previous Q wave, clinically significant liver or kidney disease (serum creatinine ≥ 2.5 mg/dL or creatinine clearance < 30 mL/min; GOT, GPT, total bilirubin, or alkaline phosphatase higher than 2.5 fold the upper normal limit of the reference ranges), hyperphosphatemia > 5.5 mEq/L, alcohol or drug abuse, or any other severe concomitant disease. Also excluded were those patients with obliged prescription of angiotensin converting enzyme inhibitors (ACEI) or with angiotensin II receptor blockers (ARB) according to clinical practice guidelines[1] or with intolerance to these drugs (by virtue of their inclusion in an additional prospective phase of this study with one of these drugs). Diabetic patients were defined as: fasting glycemia > 126 mg/dL, ≥ 200 mg/dL two hours after oral load, or any determination ≥ 200 mg/dL accompanied by symptoms, a previous diagnosis of diabetes, or patients treated with oral anti-diabetics or insulin.[14]

Baseline demographic and clinical data, cardiovascular risk factors, concomitant diseases, and used drugs were entered into the database.

Measurement of albuminuria

Initial detection of albuminuria was done by qualitative reactive deep-stick. After having documented the positivity with this method, a single quantitative determination was done (nephelometric method) by means of any of the following three procedures, according to the physician's choice: a) albumin excretion rate in 24-hour urine; b) albumin/creatinine ratio; c) albumin concentration in the first morning urine. For further analysis, patients were classified into the groups indicated in Table 1.[15]

Measurement of blood pressure

The mean systolic and diastolic blood pressure values (with an approximation of 2 mmHg) were recorded, from two readings done on the dominant arm, by the auscultatory method and with mercury sphingomanometer after 5 minutes rest and in the sitting position, in a quiet environment. Non-controlled arterial hypertension was considered if blood pressure levels were above 140/90 mmHg in the non-diabetic population and 130/80 mmHg in diabetics or if the patient was under treatment. Arterial hypertension was scaled according to European guidelines (grade 1: 140/90 - 160/100 mm Hg; grade 2: 160/100 - 180/110 mm Hg; grade 3: > 180/110 mm Hg).[2]

Statistical Analysis

Quantitative variables are presented as mean (standard deviation). Its association with dichotomous variables was analyzed by the Student's t test for means comparison of non-paired data. Categorical variables are described as percentages. P values < 0.05 were considered as being significant.

Table I. Groups of analyzed patients by results of quantitative albuminuria determination

Group	Qualitative detection	24-h urine (mg)	Morning urine (mg/min)	Albumin/ creatinine ratio (mg/g)
«Normoalbuminuria»	Positive	<30	<20	<30
«Microalbuminuria»	Positive	30-300	20-200	30-300
«Macroalbuminuria»	Positive	>300	>200	>300

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Table II. Baseline demographic and clinical data of included patients (n = 2711)

	No diabetes (n = 1.562)	Diabetes (n = 1.149)	p
Age (years)			
- Mean (range)	63.0 (10.2)	65.1 (9.7)	< 0.01
- ≥ 75 years	12.0%	16.0%	< 0.01
Men/Women	55.7%/44.3%	53.7%/46.3%	ns
BMI (kg/m^2)			
- BMI ≥ 25 kg/m^2	1.283 (82.1%)	1.002 (87.2%)	< 0.01
- BMI ≥ 30 kg/m^2	398 (25.5%)	399 (34.7%)	< 0.01
Associated heart disease			
- LVH	865 (55.3%)	645 (56.1%)	n.s.
- Ischemic	340 (21.8%)	447 (38.9%)	< 0.01
- Ictus	66 (4.2%)	92 (8.0%)	< 0.01
- AF	296 (19.0%)	241 (22.0%)	ns
Total cholesterol (mg/dL)	215.3 (39.4)	213.1 (40.3)	ns
- Total cholesterol > 200 mg/dL	993 (65.4%)	730 (64.8%)	ns
LDL-Cholesterol (mg/dL)	134.5 (32.8)	131 (34.1)	< 0.05
HDL-Cholesterol (mg/dL)	50.5 (14.2)	48.9 (14.3)	< 0.01
Triglycerides (mg/dL)	145.8 (66.5)	166.5 (79.6)	< 0.01
Baseline glycemia basal (mg/dL)	104.0 (32.0)	154.7 (47.0)	< 0.01
Hb A1c (%)	5.5 (0.9)	7.1 (1.4)	< 0.01
Creatinine clearance (mL/min)	79.8 (33.3)	72.0 (27.1)	< 0.01

Qualitative data are presented as number of cases (percentage) in each group and quantitative data as mean (standard deviation).
Abbreviations: AF= Atrial fibrillation; Hb A1c= glycosilated hemoglobin; HDL= High density lipoproteins; LVH= left ventricular hypertrophy; BMI= Body mass index; LDL= Low density lipoproteins; n.s.= not significant

RESULTS

Two thousand seven hundred and eleven patients with a mean age of 63.9 years (standard deviation = 10.1) were included. Their demographical and baseline clinical data are shown in Table 2 separated according to the presence or absence of type 2 diabetes mellitus.

Twenty-four point five percent of the included patients had non-treated arterial hypertension and 75.5% had insufficiently controlled AHT. Forty-two point three percent of the included patients showed AHT levels of grades 2 and 3.

Table 3 shows the quantitative results of albuminuria; 961 (61.5%) non-diabetic patients and 733 (63.8%) of diabetic patients had micro or macroalbuminuria. Figure 1 shows the relationship between hypertension degree and albuminuria degree in diabetic and non-diabetic patients.

Table 4 shows the treatments that patients were taking at the time of inclusion. Comparing diabetics and non-diabetics, 66% and 63%, respectively, were on antihypertensive therapy with a single drug, and only 7% were on triple drug therapy. On the other hand, 18.9% of diabetics and 28% of non-diabetics did not receive anti-hypertension treatment at the time of inclusion into the study. As AHT degree increased, percentages of antihypertensive monotherapy were progressively lower (73% in grade 1 and 41% in grade 3), and percentages of three-drug regimens were higher (5% and 19% for AHT grades 1 and 3, respectively), as well as percentages of regimens of more than three drugs (0% and 6%, respectively).

DISCUSSION

Importance of albuminuria

The results of the *KORAL-CARDIO* study indicate, for the first time in Spain, the high prevalence of macro and microalbuminuria in patients with AHT and heart diseases among patients that are not receiving RAS blocking medications, with a significantly greater association in the group of diabetic patients. The proportion of patients with micro or macroalbuminuria was 63.1% and 65% in the non-diabetic and diabetic groups, respectively. The finding in non-diabetics is highly relevant and obliges

Table III. Global results of albuminuria determinations

Methods	«Normoalbuminuria» (n = 844)	«Microalbuminuria» (n = 1.608)	«Macroalbuminuria» (n = 259)
Albumin/creatinina ratio	5.8 (6.8)	94.7 (78.7)	468.6 (629.9)
Excreetion rate (mg/min)	10.9 (11.4)	80.5 (60.7)	414.1 (131.8)
Excretion rate (mg/24 h)	12.2 (8.6)	100.1 (68.2)	795.3 (873.2)
First morning urine albumin (mg)	10.6 (8.2)	107.3 (70.7)	827.1 (1.220.4)

Values are expressed as means (standard deviation).

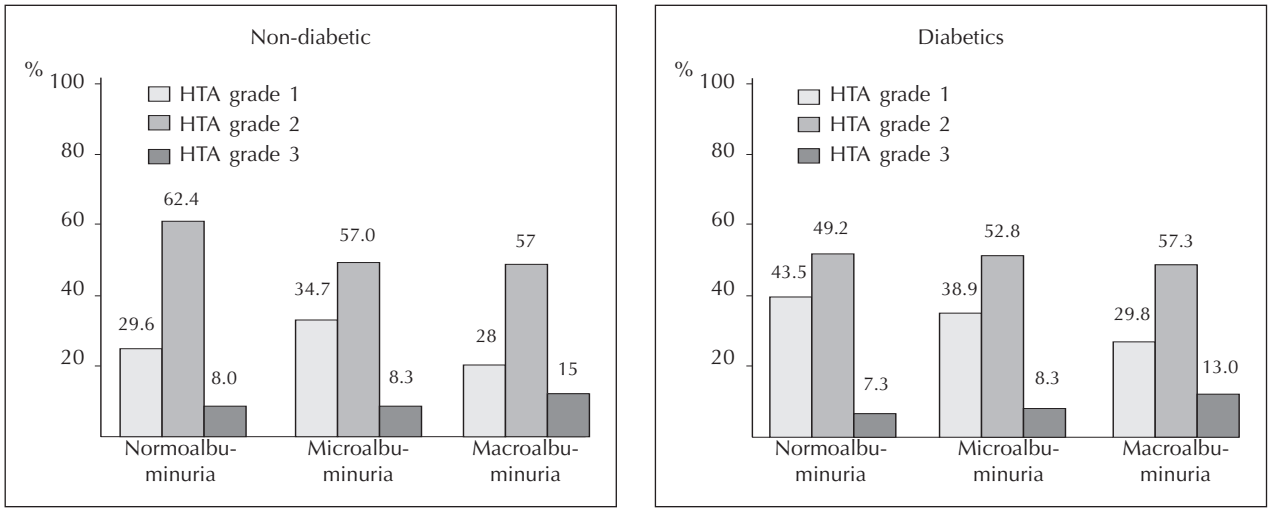

Fig. 1.—Relationship between albuminuria levels (X axis) and degrees of arterial hypertension (AHT) according to European guidelines (Y axis) (grade 1: 140/90 - 160/100 mm Hg; grade 2: 160/100 - 180/110 mm Hg; grade 3: >180/110 mm Hg) (ref. 1). The differences were significant between the three degrees of AHT in the subgroups of micro and macroalbuminuria in the non-diabetic population, and between degrees 1 and 3 in diabetics.

to the development of strategies focused on inclusion of albuminuria determination in all patients with heart diseases; although we have not found any studies about the prevalence of the use of such determination in the clinical practice in our setting, it seems reasonable to affirm that it is very infrequent.

Table IV. Treatment followed by the patients at the time of their inclusion into the study (n = 2711)

	No diabetes (n = 1.562)	Diabetes (n = 1.149)	p
Antihypertensive agents			
- None	28.0%	18.9%	< 0.01
- Diuretic	46.1%	42.2%	ns
- Beta-blocker[2]	45.9%	40.9%	< 0.05
- Calcium-channel blocker[2]	37.7%	48.5%	< 0.01
- Alpha-blocker[2]	8.1%	7.9%	ns
Number of antiypertensive agents			
- One[2]	66.4%	63.1%	ns
- Two[2]	26.2%	29.4%	ns
- Three[2]	6.6%	6.7%	ns
- Four or more[2]	0.8%	0.8%	ns
Anti-diabetic agents			
- Orals[1]	—	76.7%	—
- Insulin[1]	—	24.9%	—
Hipolipidemic aggregants[1]	41.4%	56.9%	<0.01
Platelet anti-aggregants[1]	37.4%	57.9%	<0.01

[1] Percentage of total patients in each group
[2] Percentage of total patients on antihypertensive therapy in each group.

We should highlight that patients on ACEI or ARB or those needing these drugs because of their comorbidities according to antihypertensive therapy guidelines[1,2,5] were excluded from selection. It is likely that this may have influenced on the fact that the resultant group has shown a greater degree of albuminuria, although it might also be thought that the lack of this type of therapy is by itself a marker of lesser risk, since both pharmacological groups have shown a potent antiproteinuric effect.[6-10] Although current recommendations establish the need of blocking the RAS through ACEI or ARB in patients with albuminuria, in particular in diabetic patients, the available results indicate that in routine clinical practice less that 50% of the patients receive this kind of therapy.[16] On the other hand, the proportion of diabetics in the group of patients included in the *KORAL-CARDIO* study is higher to that reported in other studies, so that our patients have a higher degree of cardiovascular and renal involvement, especially of coronary heart disease.

Hemodynamic load (increase of intraglomerular pressure) accounts for the main determinant of albumin urinary excretion in patients with mild to moderate AHT with no associated cardiovascular complications; however, in patients with advanced AHT and organic lesions, albuminuria seems to be an indicator of direct glomerular damage.[17,18]

The new clinical practice guidelines establish the need for albuminuria determination in patients with cardiovascular risk factors (especially AHT and dia-

betes). Its presence represents a powerful predictor of mortality and complications and it obliges to a stricter control of risk factors, especially of AHT: blood pressure levels lower than 130/80 mmHg should be achieved in patients with micro and macroalbuminuria, an even lower in patients with albumin excretion within the nephrotic range.[1-5] The risk of CVD increases as albuminuria range increases, which may imply that cardiovascular and renal protection through the different therapeutic interventions is directly related with the magnitude of albuminuria reduction. In this sense, a direct association between blood pressure levels reduction and albumin urinary excretion has been shown, with data suggesting that pharmacological blocking of renin-angiotensin system plays a greater antiproteinuric effect than the expected one due to its hypotensive effect.[6-10,16,19]

Several studies have analyzed the prevalence of albuminuria in the general population, the same as among hypertensive and diabetic patients, and a subgroup of patients with CVD. The different characteristics of individuals included in those studies justifies the wide disparity of the results, since prevalences ranging from 4.7% to more than 70% are observed.[17,20,21] The presence of micro and macroalbuminuria in hypertensive patients with heart diseases included in our study is higher than that described among hypertensive and diabetic patients, in particular in the subgroup of diabetic patients, which represents more than 40% of our sample.

Blood pressure control

It is worth mentioning the poor blood pressure control among included patients: a third of the cases had non-treated AHT, and the remaining two thirds had an inadequate control of blood pressure levels. Although blood pressure levels are higher than those described in previous studies of patients with CVD,[22] more than 50% of the patients included in the *KORAL-CARDIO* study had levels between 160-180/100-109 mmHg or even higher, which may be attributed to an inappropriate antihypertensive therapy not using RAS blocking drugs; both ACEI and ARB have shown hypotensive efficacy and significant clinical and prognostic benefit in patients similar to those included in our study.[6-10] In this sense, the results of the AASK study are worth mentioning showing that ramipril therapy in hypertensive patients with renal dysfunction is significantly more effective than calcium-channel blockers or beta-blockers for the prevention of glomerular filtration deterioration.[23] On the other hand, it is worth mentioning the limited use of antihypertensive medication since the proportion of patients that were not receiving any drug was considerable (28% of non-diabetics, and 18.9 of diabetics), and most of them were on a monotherapy regimen. These data should be interpreted in the setting of the characteristics of the patients included in the study (bad controlled AHT in patients with heart diseases and albuminuria, with a high proportion of diabetics), in whom the use of several antihypertensive drugs, including a RAS blocker, is necessary in order to achieve an adequate control of blood pressure levels (< 130/80 mmHg).

In agreement with the results of other studies, a high proportion of patients showed body mass indexes within the obesity range, and plasma lipid levels higher than those recommended, in particular in the group of diabetic patients.[16,20,24] Although the use of platelet anti-aggregants was significantly higher in the diabetic group, its use is far from current recommendations; however, in order to prevent the risk of hemorrhages it is necessary to reduce blood pressure levels in patients requiring these drugs, and more than 60% of the patients included in our study had levels higher than 160/100 mmHg.

Study limitations

The data of the *KORAL-CARDIO* study should be interpreted taking into account the inclusion criteria (patients with non-treated or inadequately controlled AHT and heart disease, and not receiving RAS blocking agents), which may condition the results. This is an open consecutive study, so that some "physician's clothe" bias cannot be ruled out. The proportion of diabetics is higher than that referred in studied including patients of similar characteristics, although it may be reminded that a strict methodology was followed for the diagnosis; this fact may indicate that hypertensive patients with heart diseases as the ones considered in the *KORAL-CARDIO* study (atrial fibrillation, left ventricular hypertrophy, and chronic coronary heart disease) attending the cardiology outpatient clinic would be a group with higher clinical severity that, to some extent, might justify these findings.

CONCLUSIONS

The results of the *KORAL-CARDIO* study indicate that albuminuria is very high in hypertensive, heart diseased patients that do not receive RAS blockers (ACEI or ARB), both in diabetics and in non-diabetics (so, considered as being high-risk patients). This

fact might be not only related with high blood pressure levels but also with the limited use of antihypertensive agents. This is, therefore, a marker of paramount clinical relevance that should be determined in high-risk hypertensive patients.

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