Doxazosin associated to the combination renin-angiotensin axis blocker and calcium-channel blocker in patients with chronic renal failure

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SUMMARY

Objective. *To evaluate the safety and effectiveness of the alfa-blocker doxazosin GITS in CRF patients.*

Design and methods. *The study recruited 203 CRF patients (creatinine > 1,4 mg/dl for males, creatinine > 1,2 mg/dl for females, or creatinine clearance < 80 ml/min). All patients were receiving ACE inhibitores (63.4%) or angiotensin II antagonist (36.6%) therapy but they had higher blood pressure than recommended for CRF (130/85 mmHg). Patients were clinically evaluated 1, 3 and 6 moths after starting treatment with lercanidipine (10 mg once daily). Patients with high blood pressure in spite of combined therapy with two drugs added doxazosin GITS 4-8 mg once daily to treatment.*

Result: *57 patients rendered evaluable for the study (age 64.8 ± 12.7 years, 47.4% males and 52.6 females). BP significantly decrease from 164 ± 17/92 ± 9 mmHg to 135 ± 13/78 ± 8 mmHg. 67.6% patients showed a significant BP reduction and 32.4% gets optimal BP control (< 130/85 mmHg). Two patients (3.6%) showed untoward effects. No biochemical changes were detected.*

Conclusions: *Doxazosin showed a good antihypertensive effect in CRF patients when used as third drug in resistant severe hypertension. It has a good tolerability profile and showed a neutral profile on biochemical parameters.*

Key words: ***Doxazosin. Chronic renal failure. Hypertension.***

DOXAZOSINA ASOCIADA A LA COMBINACIÓN BLOQUEANTE DEL EJE-RENINA ANGIOTENSINA Y CALCIOANTAGONISTA EN PACIENTES CON INSUFICIENCIA RENAL CR´ONICA

RESUMEN

Objetivo. *El estudio ZAFRA se diseñó para evaluar la seguridad de un nuevo bloqueante de los canales del calcio, lercanidipino, en la insuficiencia renal crónica, y*

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su posible sobre la función renal en los pacientes tratados con fármacos que bloquean el eje renina-angiotensina. Los pacientes que no controlaron su PA con estos fármacos fueron tratados con doxazosina.

Diseño y métodos. *El estudio reclutó 203 pacientes con insuficiencia renal (creatinina > 1,4 mg/dl en varones o > 1,2 mg/dl en mujeres, o aclaramiento de creatinina < 80 ml/min). Todos los pacientes estaban siendo tratados con IECA o antagonistas de receptores y la medicación se mantuvo a lo largo del estudio, sin que pudieran recibir diuréticos a lo largo del seguimiento. Los pacientes eran evaluados clínica y analíticamente 1, 3 y 6 meses después de iniciar tratamiento con lercanidipino. Aquellos pacientes que en la segunda visita no estaban controlados añadieron doxazosina GITS (4 mg en dosis única) al tratamiento.*

Resultados: *57 pacientes que iniciaron el estudio fueron tratados con doxazosina (edad media 64,8 ± 12,7 años, 47,4 varones y 52,6 mujeres). La PA se redujo significativamente desde 164 ± 17/92 ± 9 hasta 135 ± 13/78 ± 8 mmHg (p < 0,001). Se produjeron reducciones significativas de la PA en el 67,6% de los enfermos y el 32,4% de los pacientes redujeron su PA hasta los límites recomendados (<130/85 mmHg). Únicamente 2 (3,6) pacientes han presentado reacciones adversas. No se detectó aumento de la incidencia de edema. La creatinina plasmática (1,9 ± 0,6 mg/dl) no se había modificado al final del estudio (2,0 ± 0,8 mg/dl) ni el aclaramiento de creatinina (38,7 ± 15,7* vs *38,5 ± 14,5). También se detectó un descenso significativo del urato plasmático (7,0 ± 1,9* vs *6,7 ± 1,6 mg/dl, p < 0,05).*

Conclusiones: *La doxazosina ha presentado un excelente perfil de seguridad en los pacientes renales, destacando la ausencia de edemas a pesar de la insuficiencia renal de los pacientes.*

Palabras clave: ***Doxazosina. Insuficiencia renal crónica. Hipertensión arterial.***

INTRODUCTION

It is well known that the cardiovascular system is severely affected by the presence of chronic renal failure.[1] The Hypertension Detection and Follow-up Program (HDFP) study[2] showed that initial plasma creatinine levels have a prognostic value for mortality from any origin at 5 and 8 years of patient follow-up. Hypertension is also an important determinant of renal disease progression, independently of the cause of the latter. The risk for developing end-stage chronic renal failure (comparing to patients with optimal arterial blood pressure) is increased three fold when DBP reaches 90 mmHg.[3] Proteinuria presence in hypertensive patients is also a strong predictor of high morbidity and mortality from cardiovascular origin.[4] More importantly, strict blood pressure control is the main mechanism to prevent progression to chronic renal failure, and thus, it is recommended in most of the therapeutic guidelines.[5,6]

Anti-hypertensive agents that block the renin-angiotensin axis, such as ACEIs and angiotensina receptor antagonists (ARA) seem to have a protector role, besides its hypotensive effect, and their use has been recommended for renal disease.[5] By contrast, the renoprotective effect of calcium channel blockers is controversial, in spite of experimental data that suggested this capability.[6] In this sense, it has been suggested that calcium channel blockers may improve renal function in patients previously treated with ACEIs.[7] The ZAFRA study was aimed at assessing the safety and efficacy of lercanidipine in patients with chronic renal failure, and secondarily the potential renoprotective effect of calcium channel blockers.[8]

A specific objective was to assess edema incidence, a complication less frequent with lercanidipine treatment, in a group of patients with a tendency to water-salt retention, as do patients with renal failure. Recently, the ALLHAT study has raised some concern with the use of doxazosin in hypertensive patients due to the increase of the incidence of cardiac failure in the diuretics-treated arm.[9] This article comprises the results of the subgroup of patients from the ZAFRA study that were treated with doxazosin due to poorly control blood pressure in spite of combined treatment with lercanidipine and ACEI or ARA with no diuretic treatment.[8]

DESIGN AND METHODS

Two hundred and three patients were recruited, meeting the criteria of being hypertensive, suffering

from renal failure, and having BP > 130/85 mmHg in spite of treatment with ACEI or angiotensin receptor antagonist. Patients were not allowed to be treated with diuretics or other hypotensive drugs before the study beginning. The protocol was presented to and approved by the Clinical Trials Committee of the Fundación Puigvert of Barcelona. Chronic renal failure was defined by presence of plasma creatinine ≥ 1.4 in male and ≥ 1.2 in female patients, or creatinine clearance < 80 mL/min. All patients were on ACEI treatment (67.4%) or angiotensin receptor antagonists (32.6%), at appropriate doses (equal or similar to 20 mg/d of enalapril). All patients had arterial hypertension in spite of treatment with renin-angiotensin axis blockers, defined by recommendations of the WHO-HIS Clinical Guidelines for renal patients (SBP ≥ 130 and/or DBP ≥ 85 mmHg).

Lercanidipine treatment was started at a 10-mg dose in a single daily intake. Patients were followed for 4 months according to a four-visits schedule (inclusion, 1, 3, and 6 months). When the blood pressure goal was not reached at the first month visit, treatment with alpha- or beta-blockers was added. Use of diuretics was not allowed throughout the study to avoid interference with edema assessment. In that case, patients were scheduled for a visit with faculty staff within 30 days (2 months). If blood pressure persisted elevated, patients could be excluded, according to the investigator's clinical judgment. BP and pulse rate were taken at each visit, and patients were asked about the presence of symptoms and adverse events, and about adherence to treatment. BP was measured with a mercury sphingomanometer, in a sitting position, approximately 24 hours after the last medication intake, with two measurements with a 3-minutes interval aside. Blood samples were also collected at each visit for biochemical determinations (including creatinine), and 24-hour urine (to measure creatinine clearance, proteinuria, and microalbuminuria). A blood count was also performed.

Slow-releasing doxazosin treatment (4 mg in a single daily dose) was prescribed to 51 patients at the first month follow-up visit, according to treatment schedule. Six additional patients started doxazosin treatment at the third month visit; these patients have been included in the tolerability analysis, but have been excluded from the anti-hypertensive efficacy analysis. Doxazosin-treated patients were 27 men and 30 women, with a mean age of 64.8 ± 12.7 years.

An independent company performed the statistical analysis of the data. Data have been presented as mean ± standard deviation. The differences between continuous variables were compared by means of Student's t test for related samples. The differences in frequency values were compared by means of the McNemar test because of paired values.

Table I. Arterial blood pressure changes

	SBP	DBP	PR
Baseline	164.2 ± 17.3	91.6 ± 9.1	76.4 ± 11.1
1 month	151.3 ± 13.9*	86.0 ± 8.2*	75.6 ± 9.7
3 months	137.7 ± 14.1*	79.9 ± 8.0*	75.5 ± 9.6
6 months	134.7 ± 12.4*	78.4 ± 7.8*	75.1 ± 7.2

*SBP and DBP expressed in mmHg, PR in heat bits per min. Doxazosin was introduced within the first month.

RESULTS

After one month of treatment, SBP and DBP significantly decreased with lercanidipine (from 151.3 ± 13.9 / 86.0 ± 8.2 to 144.9 ± 16.8 / 81.0 ± 7.6 mmHg; $p < 0.001$). The addition of doxazosin achieved a further decrease in BP levels at the following visits (see values in Table I). At the 6th month, mean BP decrease from baseline values was –16.4 / -6.3 mmHg (relative reduction 10.0 / 8.1%). There were no significant differences in pulse rate (Table I). At the end of the follow-up period, the percentage of patient that had reached BP goal (optimal control, BP < 130/85 mmHg) was 32.4%, and 50.0% had favorably responded to administration of the drug without reaching the BP goal (fig. 1). 38.2% of the patients achieved a suboptimal control (BP ≤ 130/85 mmHg).

Doxazosin treatment did not induce significant changes in hematological values. Progression of evaluated biochemical parameters is shown in Table II. There were no changes in cholesterol and triglycerides. There were no observed changes in plasma urea and creatinine levels, or in creatinine clearance. Uricemia significantly decreased at the third and sixth months ($p < 0.05$). There were no changes in proteinuria either.

A total of 22 patients discontinued treatment because of poor adaptation to it (n = 1), poor BP control in spite of treatment (n = 18=, and treatment withdrawal (n = 3). Two patients (3.5%) notified adverse events during the treatment period (erectile dysfunction in one case, and urinary incontinency in another). No patient complained about edema or lower limb heaviness, and edema was not detected at the patients' clinical inspection performed at each visit.

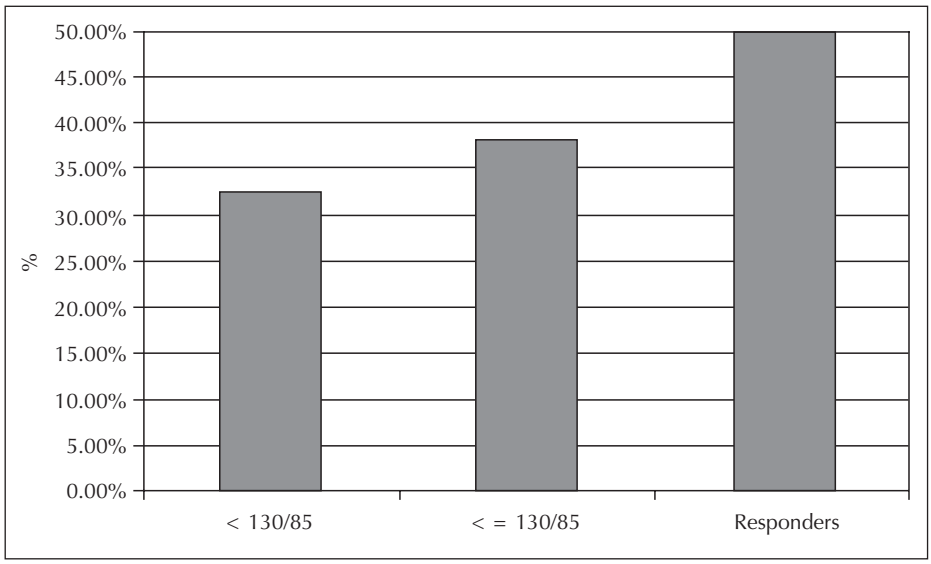

Fig. 1.—Number of controlled patients and responders at the end of the follow-up period; p < 0.001 as compared to month 1 (McNemar's test). Responder is considered when SBP decreases > 10 mmHg or DBP > 5 mmHg.

DISCUSSION

Doxazosin, an alpha-1 receptor antagonist, seems to be an effective and safe agent in patients with renal failure when used in combination with drugs that block the renin-angiotensin axis and with calcium channel blockers. This is the first published study on the safety of this association and the largest studied sample on the clinical effects of doxazosin in renal failure. There are few studies on doxazosin safety in chronic renal failure. Generally, the adverse events are few and there is no need for dose reduction or treatment discontinuation, since pharmacokinetics is not modified. Plasma renal flow is not modified, but the effects on glomerular filtration are less known and may occur with mild decreases of the former.[10-14] Our study results are in agreement with what had been published, confirming this in a large series of patients.

Table II. Biochemistry values changes

	Baseline	1 month	3 months	6 months	Units
Creatinine	1.9 ± 0.6	1.9 ± 0.5	1.9 ± 0.6	2.0 ± 0.8	mg/dL
Urea	70.0 ± 34.6	70.5 ± 32.4	79.5 ± 28.3	80.3 ± 30.3	mg/dL
Urate	7.0 ± 1.9	6.6 ± 1.5	6.4 ± 1.7#	6.7 ± 1.6#	mg/dL
Cholesterol	209 ± 47	207 ± 36	210 ± 32	202 ± 36	mg/dL
Triglycerides	139 ± 47	139 ± 54	141 ± 46	138 ± 44	mg/dL
Glucose	111 ± 39	114 ± 41	105 ± 22	104 ± 36	mg/dL
Proteinuria	0.9 ± 0.7	0.9 ± 0.8	0.8 ± 0.6	0.8 ± 0.8	g/24 h
Cr. Clearance	38.7 ± 15.7	40.9 ± 18.5	40.0 ± 15.3	38.5 ± 14.5	mL/min

#p < 0.05 from baseline. Doxazosin was given within the firts month.

Alpha-1 adrenergic antagonists seem to produce water-salt retention. In 1984, increase of plasma volume, interstitial volume, and extracellular volume was detected after treatment with prazosin, both in a short and long term.[15] Other studies found weight increase as well as biochemical changes compatible with volume expansion due to prazosin.[16,17] In the Veteran Administration Cooperative Study on Anti-hypertensive Agents a significant weight increase was observed within 8 weeks of follow-up in the group treated with prazosin, as compared to both baseline weight and weight changes in the other groups (that were inexistent or showed a decrease in body weight). However, mean weight gain from baseline was not significant within one year of follow-up. Patients treated with terazosin also showed a tendency to gain weight (approximately 1 kg), whereas those on placebo lost weight.[19] Similarly, in two randomized trials that included a wash-out period of the active treatment with alpha-1 antagonists, it was shown that a mean loss of 1.3 kg occurred after discontinuation of the drug.[20]

Doxazosin has also been associated to volume expansion. One study demonstrated body fluid volume expansion of about 10% from baseline values.[21] Some larger trials have shown that doxazosin treatment may induce some weight gain, but the Treatment of Mild Hypertension Study (TOMHS), the largest controlled trial performed with doxazosin, is a remarkable exception. This study did not find any body weight change. The five treatment groups received comprehensive dietary counseling for loosing weight and, likely as a result of this, weight reduc-

tion was homogeneous among the different study arms.[22]

The final report on the doxazosin arm of the ALLHAT study presented unexpected outcomes, due to the potential association between diuretics use and the risk for sudden death,[23] and the favorable effect of alpha-1-adrenergic antagonists on plasma cholesterol and triglycerides levels.[22] The ALLHAT study showed a significant increase in the incidence of heart failure (almost twice) in the doxazosin-treated group in comparison with those treated with chlorthalidone. However, there were no differences in the primary end-point (outcomes in ischemic heart disease) or in the secondary end-point of global mortality. Since renal failure is a disease in which there is a tendency to overhydration and edema occurrence, the ALLHAT outcomes raised a number of questions about doxazosin safety in renal failure patients, not as much with regards to occurrence of heart failure as to the chance of water-salt retention occurrence, which most frequent clinical manifestation is edema formation. In this sense, follow-up studies published with doxazosin in renal failure patients have short, both in follow-up time and in number of included patients. Our data do not show any increase in the incidence of edema or fluid retention in renal failure patients. No heart failure episodes were detected either, although some adverse effects were noticed on the urinary tract.

It has been suggested that heart failure occurrence in the doxazosin-treated group in the ALLHAT study was only the expression at the beginning of treatment of a latent condition that controlled with diuretics. It is important to know that 90% of the recruited patients to each group were switched from the hypotensive treatment they were already receiving.[24] The design of the ZAFRA study excluded recruitment of patients on diuretic treatment in order to avoid masking the occurrence of edema in the patients; for the same reason, diuretic treatment was not allowed during the follow-up. This is an important difference with the doxazosin arm of ALLHAT study, where most of the patients were previously treated with diuretics. Our results, with a shorter follow-up period than ALLHAT, seem to indicate that in renal failure patients not previously treated with diuretics, doxazosin treatment, assessed from a clinical perspective, does not produce clinically detectable body water retention.

The degree of control required for renal failure patients (130/85 mmHg at the time of study designing) usually requires the use of several drugs simultaneously for BP control.[30] In spite of this, the degree of blood pressure control in renal patients is far from being optimal usually, as stated in COPARENAL study, carried out in our country but yet not published, where < 17% of the patients reach a SBP < 130 mmHg.[31] In this sense, the efficacy of the triple combination used in this study may be considered as good, in spite of not having included diuretic drugs, a type of drugs especially indicated as hypotensive in this type of patients.[32]

In summary, doxazosin has shown good efficacy as anti-hypertensive agent in renal failure patients. The incidence of adverse events was very low, among which there were no cases of overhydration, even with diuretics forbidden.

REFERENCES

1. Rostand SG, Brunzell JD, Cannon RO, Victor RG: Cardiovascular complications in renal failure. *J Am Soc Nephrol* 2: 1053-1058, 1991.
2. Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, Schneider KA: prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the Hypertension Detection and Follow-up Program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension* 13 (Supl. 5): 1180-1193, 1989.
3. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J: Blood pressure and end-stage renal disease in men. *N Engl J Med* 334: 13-18, 1996.
4. Samuelsson O, Wilhelmsen L, Elmfeldt D, Pennert K, Wedel H, Wikstrand J, Pennert K, Wedel H, Wikstrand J, Berglund G: Predictors of cardiovascular morbidity in treated hypertension: results from the Primary Preventive Trial in Göteborg, Sweden. *J Hypertens* 3: 167-176, 1985.
5. Ruilope LM, Campo C, Rodriguez-Artalejo F, Lahera V, García-Robles R, Rodicio JL: Blood pressure and renal function: Therapeutic implications. *J Hypertens* 14: 1259-1263, 1996.
6. Tobbe S, Epstein M: The use of calcium antagonists in the treatment of hypertensive persons with kidney disease. *Current Hypertension Reports* 4: 191-194, 2002.
7. Bitar R, Flores O, Reverte M, López-Novoa JM, Macias JF: beneficial effect of verapamil added to chronic ACE inhibitor treatment on renal function in hypertensive elderly patients. *Int Urol Nephrol* 32 (2): 165-169, 2000.
8. Robles NR, Ocón J, Gómez Campderá F, Manjón M, Pastor L, Herrera J y cols.: Lercanidipine in chronic renal failure patients. The ZAFRA study. *Renal Failure* 27: 81-88, 2005.
9. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: t he Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Am Med Assoc* 283: 1967-1975, 2000.
10. Waller DG, Oliver RM: Doxazosin in renal impairment. *J Hum Hypertens* 4 (Supl. 3): 47-49, 1990.
11. Carlson RV, Bailey RR, Begg EJ, Cowlishaw MG, Sharman JR: Pharmacolinetics and effect on blood pressure of doxazosin in normal subjects and patients with renal failure. *Clin Pharmacol Ther* 40: 561-566, 1986.
12. Anderton JL, Notghi A: An evaluation of the efficacy and safety of doxazosin in the treatment of hypertension associated with renal insufficiency. *J Hum Hypertens* 4 (Supl. 3): 52-57, 1990.

13. Mori Y, Matsubara H, Nose A, Shibasaki Y, Masaki H, Kosaki A y cols.: Safety and availability of doxazosin in treating hypertensive patients with chronic renal failure. *Hypertens Res* 24: 359-363, 2001.
14. Bartels AC, De Vries PM, Oe LP, Van Bronswyk H, Donker AJ, Reveillaud RJ y cols.: Doxazosin in the treatment of patients with mild or moderate hypertension and mild or moderate renal insufficiency. *Am Heart J* 116 (6 Pt 2): 1772-1777, 1988.
15. Bauer JH, Jones LB, Gaddy P: Effects of prazosin therapy on BP, renal function, and body fluid composition. *Arch Intern Med* 144: 1196-1200, 1984.
16. Deger G: Comparison of the safety and efficacy of once-daily terazosin *versus* twice-daily prazosin for the treatment of mild to moderate hypertension. *Am J Med* 80: 62-67, 1986.
17. Letcher RL, Chien S, Laragh JH: Changes in blood viscosity accompanying the response to prazosin in patients with essential hypertension. *J Cardiovasc Pharmacol* 1: S8-S20, 1979.
18. Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ: Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Circulation* 95: 2007-2014, 1997.
19. Bryson CL, Psaty BM: A Review of the Adverse Effects of Peripheral Alpha-Antagonistsin Hypertension Therapy. C*urr Control Trials Cardiovasc Med* 3: 7-9, 2002.
20. Ruoff G: Effect of withdrawal of terazosin therapy in patients with hypertension. *Am J Med* 80: 35-41, 1986.
21. Lund-Johansen P, Omvik P, Haugland H: Acute and chronic haemodynamic effects of doxazosin in hypertension at rest and during exercise. *Br J Clin Pharmacol* 21 (Supl. 1): 45S-54S, 1986.
22. Neaton JD, Grimm RH Jr, Prineas RJ, Stamler J, Grandits GA, Elmer PJ y cols.: Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. *JAMA* 270: 713-724, 1993.
23. Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin X y cols.: Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 330: 1852-1857, 1994.
24. Krakoff LR: Comments on ALLHAT and doxazosin. Curr Control Trials Cardiovasc. *Med* 2: 254-256, 2001.
25. The CONSENSUS Trial Study Group: Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 316: 1429-1435, 1987.
26. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F y cols.: A comparison of enalapril eith hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 325: 303-310, 1991.
27. Pitt B, Segal R, Martínez FA, Meurers G, Cowley AJ, Thomas I y cols.: Randomised trial of losartan *versus* captopril in patients over 65 with heart failure (Evaluation of losartan in the elderly study, ELITE). *Lancet* 349: 747-752, 1997.
28. Pitt B, Poole-Wilson PA, Segal R, Martínez FA, Dickstein K, Camm AJ y cols.: Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial-The Losartan Heart Failure Survival Study ELITE II. *Lancet* 355: 1582-1588, 2000.
29. Cohn JN, Tognoni G: The effect of the angiotensin receptor blocker valsartan on morbidity and mortality in heart failure. *N Engl J Med* 345: 1667-1675, 2001.
30. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S y cols.: for the HOT study group: effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 351: 1755-1762, 1998.
31. Marín R, Fernández-Vega F, Alcázar JM, Aranda P, Díez J, Gorostidi M y cols., en representación de los investigadores del Estudio Coparenal: grado de control de la hipertensión arterial en pacientes con insuficiencia renal crónica atendidos en consultas externas de nefrología. Estudio Coparenal. XXXIV Congreso Nacional de la SEN. *Nefrología* 24 (Supl. 10), 2004.
32. Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *Journal of Hypertension* 21: 1011-1053, 2003.