

Losartan reduces microalbuminuria in hypertensive microalbuminuric type 2 diabetics

Jose V. Lozano, Jose L. Llisterri¹, J Aznar² and Josep Redon on behalf of a Spanish Working Group

Hypertension Clinic, Internal Medicine, Hospital Clinico, Valencia,¹University of Valencia Health Care Centre of Vallada and ²Hospital Marina Alta, Denia, Spain

Abstract

Background. The aim of the present study was to assess the antialbuminuric effect of losartan in a large number of hypertensive type 2 diabetics.

Methods. This was a 6-month, open-label, prospective and multicentre study. A total of 422 patients with type 2 diabetes who were hypertensive [sitting systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg] and microalbuminuric [urinary albumin excretion (UAE) 30–300 mg/day] were eligible for the study. After a 2-week run-in period, patients were placed on losartan 50 mg once a day. If the BP did not reach the desired goal ($< 140/90$ mmHg) after a 4-week period, the losartan dose was doubled. In the absence of control of BP, losartan 50 mg/day + hydrochlorothiazide 12.5 mg/day was administered. Initially and at 12 and 24 weeks of active treatment, BP, UAE, HbA_{1c} and other renal function parameters were evaluated.

Results. A significant decrease in SBP and DBP was observed, as well as in parameters reflecting metabolic control, fasting glucose and HbA_{1c}. UAE also decreased significantly, but the percentage of the variance of change in UAE explained by the changes in SBP and HbA_{1c} was, however, negligible, i.e. 4%. Moreover, small but significant reductions in uric acid, total cholesterol and triglycerides, and an increase in HDL-cholesterol levels were also observed.

Conclusion. Antihypertensive treatment with losartan exerts a beneficial effect on UAE, a benchmark for measuring the efficacy of therapeutic interventions in diabetic nephropathy, by reducing BP and allowing better diabetes control. The role of other mechanisms influencing the favourable outcome, beyond these measured effects, needs to be assessed in further studies.

Keywords: diabetes; hypertension; losartan; microalbuminuria

Introduction

Because of the ageing of the population, an increasing prevalence of obesity and sedentary life habits, the prevalence of type 2 diabetes is increasing [1]. This type of diabetes is associated with a marked increase in the risk of cardiovascular disease. Hypertension, frequently found in patients with diabetes with a prevalence approximately twice that of the non-diabetic population [2], further increases the already high risk of cardiovascular disease associated with type 2 diabetes [2–4].

By the time patients are diagnosed with type 2 diabetes, many have already developed hypertension, microalbuminuria or even macroalbuminuria, and cardiovascular disease [3,5,6]. Microalbuminuria, that is present in a quarter of the patients at the time of diagnosis, is a strong predictor of all-cause mortality and of cardiovascular morbidity and mortality. Although the mechanism underlying the association between microalbuminuria and mortality is not clear, the presence of microalbuminuria may reflect a generalized defect in vascular permeability leading to atherogenesis [7]. Hypertension is a major risk factor for the development of microalbuminuria [8].

The main goal of any treatment for patients with type 2 diabetic nephropathy should be to prevent the natural progression from microalbuminuria to macroalbuminuria and to end-stage renal disease, and to reduce cardiovascular morbidity and mortality. Effective antihypertensive treatment is the best inhibitor of diabetic nephropathy [9]. Since reducing albuminuria delays progression of diabetic nephropathy, this parameter can be used as a benchmark for measuring the efficacy of therapeutic interventions [10]. Angiotensin II has been implicated in the progression of

Correspondence and offprint requests to: Josep Redon, Hypertension Clinic, Hospital Clinico, Avda Blasco Ibañez, 17, 46010 Valencia, Spain.

renal failure in diabetic nephropathy [11]. Blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACEIs) [12,13] may reduce albumin excretion more than other agents in patients with type 2 diabetic nephropathy, but their effect on the glomerular filtration rate (GFR) may be similar [14]. Losartan, an antagonist of the AT₁ angiotensin II receptor (ARAI), has been shown to induce changes in renal haemodynamics and proteinuria similar to those induced by the ACEI enalapril, indicating that the antiproteinuric effect of ACE inhibition is mediated primarily by RAS blockade [15,16].

The aim of the present study was to assess the antialbuminuric effect of losartan in a large number of hypertensive type 2 diabetics. Furthermore, the relationship between changes in the blood pressure and changes in the urinary albumin excretion (UAE) were analysed.

Patients and methods

This was a 6-month, open-label, prospective and multicentre study. Patients with type 2 diabetes who were hypertensive [sitting systolic blood pressure (SBP) \geq 140 mmHg and/or diastolic blood pressure (DBP) \geq 90 mmHg] and microalbuminuric (UAE 30–300 mg/day) were eligible for the study. Exclusion criteria were: (i) patients with secondary hypertension; (ii) those without pharmacological treatment or receiving a combination of two or more antihypertensive drugs; (iii) those with congestive heart failure (NYHA class III or IV); (iv) serum creatinine $>$ 2 mg/dl; and (v) known hypersensitivity or intolerance to losartan.

After a 2-week run-in period, patients were placed on losartan 50 mg once a day. If the BP did not reach the desired goal ($<$ 140/90 mmHg) after a 4-week period, the losartan dose was doubled. In the absence of control with losartan 100 mg/day, losartan 50 mg/day + hydrochlorothiazide 12.5 mg/day was administered to achieve the desired BP. Interview and physical examination assessed side effects, concomitant diseases and blood pressure at each visit during the treatment. All patients were counselled to follow a low sodium and balanced carbohydrate diet, and investigators were instructed to maintain, if possible, the same antidiabetic therapy throughout the complete study.

Blood pressure was measured using a mercury sphygmomanometer with the patient in the sitting position after 5 min of rest in a quiet environment, following the recommendations of the British Hypertension Society [17]. SBP and DBP (Korotkoff phase I and phase V, respectively) were the mean of three readings measured at 10-min intervals.

Initially, UAE was assessed using a semiquantitative method (Micral-test, Boehringer Mannheim) on three first-morning urine samples. If at least two were positive (\geq 50 μ g/ml), a 24-h urine collection was obtained and UAE was measured using an immunonephelometric assay (Behring Institute). Aliquots of urine were taken from the 24-h sample in glass tubes at 4°C and were analysed 1–7 days after collection.

Microalbuminuria, glycosylated haemoglobin, serum lipids, routine haematological and blood chemistry analyses (haematological indices, blood glucose, serum sodium and potassium concentrations, liver enzyme levels, uric acid, urea

and creatinine concentrations) were done at baseline, and at 12 and 24 weeks of active treatment.

For each variable, the values were expressed as mean \pm SD. The UAE data were analysed as a continuous variable with logarithmic transformation. Assessment of changes in variables over time was performed by paired *t*-test. Pearson correlation coefficients were used to examine the linear relationship between the changes in logUAE and the changes in BP or glycosylated haemoglobin. The independent association between these variables and logUAE was examined by multivariate regression analysis. *P*-values $<$ 0.05 were considered significant.

The drug treatment was well tolerated, and secondary effects that result in drug withdrawal were observed in only 1.2% of the subjects.

Results

From a total of 445 patients recruited, 424 were suitable for the analysis. The general characteristics of the study population are summarized in Table 1. Twenty-two percent of the patients were diagnosed recently and had not received previous antihypertensive therapy, 25% were treated with an ACEI, 24% with calcium channel blockers, 15% with diuretics, 9% with β -blockers, and 5% with other drug classes. During the treatment period, SBP control was achieved in 70% of the patients, 23% of them after the addition of hydrochlorothiazide. Diastolic BP was controlled in 82% of the patients, 20% after the addition of the diuretic.

The impact of treatment on body weight, BP values, HbA_{1c}, UAE and other parameters is shown in Table 1. A significant decrease in SBP and DBP was observed, as well as in parameters reflecting metabolic control, fasting glucose and HbA_{1c}. This improvement in BP and metabolic control was followed by a significant reduction in UAE (from 115 \pm 85 mg/24 h to 66 \pm 55 mg/24 h, *P* $<$ 0.0001). One hundred and seven patients (25%) normalized their microalbuminuria. Moreover, small but significant reductions in uric acid, total cholesterol and triglycerides, and an increase in HDL-cholesterol levels were also observed.

The change in UAE over time was weakly, although significantly, correlated with the changes in SBP

Table 1. Blood pressure, urinary albumin excretion and metabolic parameters at baseline and after 6 months treatment with losartan in hypertensive and microalbuminuric type 2 diabetics

	Baseline	Six months	<i>P</i>
Weight (kg)	75 \pm 11	74 \pm 10	0.001
SBP (mmHg)	160 \pm 13	137 \pm 8	0.001
DBP (mmHg)	96 \pm 7	82 \pm 6	0.001
UAE (mg/24 h)	115 \pm 85	66 \pm 55	0.001
Glucose (mg/dl)	155 \pm 44	140 \pm 30	0.001
HbA _{1c} (%)	7.0 \pm 1.5	6.6 \pm 1.26	0.001
Uric acid (mg/dl)	5.8 \pm 1.4	5.5 \pm 1.2	0.001

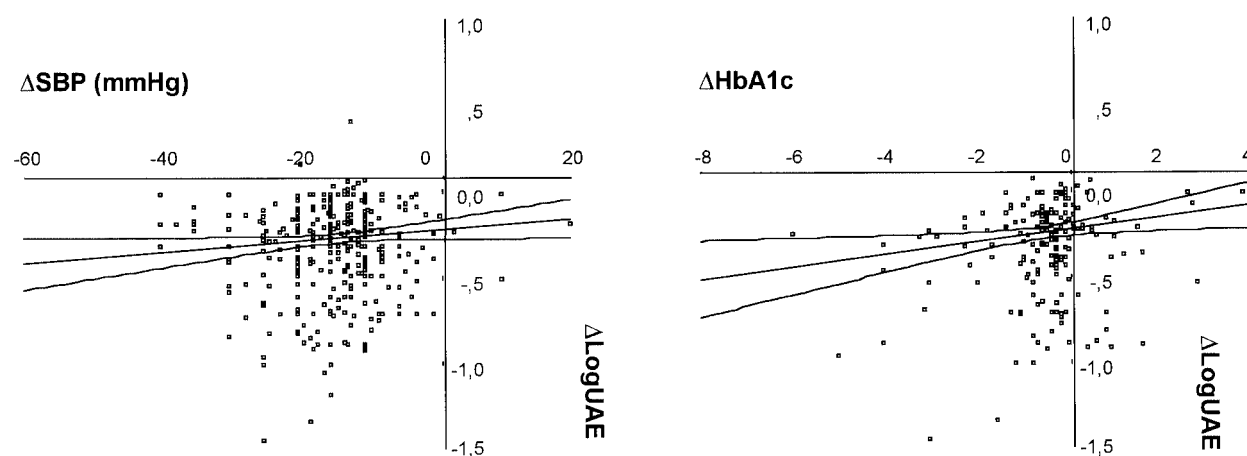


Fig. 1. Regression line, and the 95% confidence interval, between changes in logUAE and SBP (left panel) and in HbA_{1c} (right panel).

($r=0.18$, $P<0.01$), DBP ($r=0.13$, $P<0.05$) and HbA_{1c} ($r=0.15$, $P<0.05$) (Figure 1). When a multiple regression analysis was performed using as a dependent variable the change in logUAE, the changes in SBP and HbA_{1c} were independently significant parameters. The percentage of the variance of change in UAE explained by the changes in SBP and HbA_{1c} was, however, negligible, at 4%.

Discussion

In a large group of hypertensive, microalbuminuric, type 2 diabetics, losartan reduced BP values and UAE during a 6-month period of treatment. The administration of losartan permits a significant improvement in metabolic parameters, mainly those reflecting carbohydrate (baseline glucose, HbA_{1c}) and lipid (triglycerides, HDL-cholesterol) metabolism. A small but significant reduction is also observed in uric acid levels.

The main factor influencing the observed reduction in UAE during the losartan treatment might be BP reduction. Clinical trials have demonstrated the effect of various antihypertensive agents on proteinuria in patients with diabetes. In a meta-analysis of 100 controlled and uncontrolled trials, the relative effect of different antihypertensive agents on proteinuria was assessed [12]. Although treatments with ACEIs, calcium antagonists and β -blockers has a similar effect on mean arterial BP, the greatest reduction in UAE occurred in patients treated with ACEIs. A second meta-analysis, however, challenged the hypothesis and suggested that at maximal antihypertensive doses there was no significant difference between the antiproteinuric effects of ACEIs and those of other antihypertensive drugs [18]. Thus, whether the effects of ACEIs on renal function in patients with diabetes are unique to this class of agent or represent a non-specific effect of BP reduction remains controversial.

Losartan, whose antihypertensive activity is due to the selective antagonism of angiotensin II at the AT₁ receptor, has been shown to induce changes in renal haemodynamics and proteinuria similar to those induced by the ACEI enalapril, indicating that the antiproteinuric effect of ACE inhibition is mediated primarily by RAS blockade [15,16]. In the present study, the weak correlation observed between changes in logUAE and changes in BP values indicated that other factors may be involved in UAE reduction.

Among those factors, the improvement of diabetes control should be mentioned. Adequate metabolic control is a key point in the treatment of diabetic patients. The impact of HbA_{1c} reduction on UAE has been demonstrated in the UKPDS [19], and in the present study a significant change was observed during antihypertensive treatment with losartan. A neutral or positive effect of losartan on insulin resistance has been found, allowing a better diabetes control.

Finally, the beneficial effect of specific RAS blockade, other than BP and HbA_{1c} reduction, needs to be considered. Angiotensin II has been implicated in the progression of renal failure in diabetic nephropathy [11], up-regulating the expression of growth factors and cytokines such as transforming growth factor- β 1, tumour necrosis factor- α , osteopontin, vascular cell adhesion molecule 1, nuclear factor- κ B, platelet-derived growth factor, fibroblast growth factor and insulin-like growth factor [20,21]. Losartan reduces the increased levels of some of these growth factors and cytokines [20].

In summary, antihypertensive treatment with losartan exerts a beneficial effect on UAE, a benchmark for measuring the efficacy of therapeutic intervention in diabetic nephropathy, by reducing BP and allowing better diabetes control. The role of other mechanisms influencing the favourable outcome, beyond these measured effects, needs to be assessed in further studies.

References

1. Grundy SM, Benjamin IJ, Burke GL, Smith S Jr, Fuster V. Diabetes and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. *Circulation* 1999; 100: 1134–1146
2. Epstein M, Sowers JR. Diabetes mellitus and hypertension. *Hypertension* 1992; 19: 403–418
3. The Hypertension in Diabetes Study Group (HDS). Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. *J Hypertens* 1993; 11: 309–317
4. The Hypertension in Diabetes Study Group. Hypertension in diabetes study (HDS): II. Increased risk of cardiovascular complications in hypertensive type 2 diabetic patients. *J Hypertens* 1993; 11: 319–325
5. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med*. 1984; 310: 356–360
6. American Diabetes Association. Diabetic nephropathy. *Diabetes Care* 1998; 21 [Suppl 1]: S50–S53
7. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. *Arch Intern Med* 1997; 157: 1413–1418
8. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998; 317: 703–713
9. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993; 118: 577–581
10. Rossing P, Hommel E, Smidt UM, Parving H-H. Reduction in albuminuria predicts diminished progression in diabetic nephropathy. *Kidney Int* 1994; 45 [Suppl]: S145–S149
11. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 1986; 77: 1925–1930
12. Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med* 1993; 118: 129–138
13. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329: 1456–1462
14. Lacourciere Y, Nadeau A, Poirier L, Tancrede G. Captopril or conventional therapy in hypertensive type II diabetics: three-year analysis. *Hypertension* 1993; 21: 786–794
15. Gansevoort RT, de Zeeuw D, de Jong PE. Is the antiproteinuric effect of ACE inhibition mediated by interference in the renin-angiotensin system? *Kidney Int* 1994; 45: 861–867
16. Perico N, Remuzzi A, Sangalli F, Azzollini N, Mister M, Ruggenenti P, Remuzzi G. The antiproteinuric effect of angiotensin antagonism in human IgA nephropathy is potentiated by indomethacin. *J Am Soc Nephrol* 1998; 9: 2308–2317
17. Petrie JC, Ó'Brien ET, Littler WA, de Swiet M. British Hypertension Society. Recommendations on blood pressure measurement. *Br Med J* 1986; 293: 611–615
18. Weidmann P, Schneider M, Bohlen L. Therapeutic efficacy of different antihypertensive drugs in human diabetic nephropathy: an updated meta-analysis. *Nephrol Dial Transplant* 1995; 10 [Suppl 9]: 39–45
19. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes: UKPDS 33. *Lancet* 1998; 352: 837–853
20. Campistol JM, Iñigo P, Jimenez W, Lario S, Clesca PH, Oppenheimer F, Rivera F. Losartan decreases plasma levels of TGF-beta1 in transplant patients with chronic allograft nephropathy. *Kidney Int* 1999; 56: 714–719
21. Klahr S, Morrissey JJ. The role of vasoactive compounds, growth factors and cytokines in the progression of renal diseases. *Kidney Int* 2000; 57 [Suppl 75]: S7–S14

Appendix

In addition to the authors, the study institutions and investigators were as follows. Almería: Consultorio de Aguadulce—P. Calero, A. Hervás; C. S. La Cañada—J. Vailes; Consultorio de la Marinas—J. Baron Carrillo; C. S. La Cañada—M. A. Fernández. Burgos: C. S. Dr Cristobal Acosta—M. Rodríguez Correa, B. Angulo Fernández de Larrea; Villasur de Herreros—J. R. Gascón Hortelano. Cantabria: C. S. Mataporquera—P. Echave Ceballos. Córdoba: Consultorio de Hinojosa del Duque—J. M. Sánchez Hernández; Ambulatorio La Higuera—J. C. Calvo de Mora; Ambulatorio Burell—M. Aguirre Muñoz; C. S. Fuenteovejuna—G. Bueno Ferrer; C. S. Fuensanta—A. Valverde León; Ambulatorio Sector Sur—E. Lara Almirón; Consultorio La Guajarrosa—J. González Aguilar; C. S. Peñarroya—J. Guillermo Rivas Cano; C. S. Cabra—R. Rodríguez Cruz; C. S. Montilla—J. Bautista Delgado Carrillo; C. S. Lucena—A. Arjona Varo; Ambulatorio Sector Sur—J. González Aguilar. Gijón: Casa del Mar—N. Valdés Gallego, M. Miranda Suárez; Centro de Salud de El Llano—A. Beristain Urquiza, R. Uribelarra García. Granada: C. S. Huetor Vega—F. Villena Martín; C. S. Maracena—J. Morales Ortega; Consultorio de Lanjarón—P. P. Quispe Mamani; C. S. Peligros—M. A. Maldonado Laroque; Ambulatorio Góngora—J. F. Castro Pérez; C. S. Maracena—A. Penada García; Consultorio Benalúa de la Villas—D. García; Consulta Dr Cruz López—F. Cruz López; Médico Empresa Dhul—J. M. Domínguez; Ambulatorio Gran Capitán—L. Mezquita Bernad, H. Aomar. Guipuzcoa: Ambulatorio Beraun—A. Etxezortu. Jaen: Consultorio S. O. E.—C. Gómez Villalba; C. S. Virgen del Gavellar—J. Poza Herrera; C. S. Virgen de la Capilla—E. Suarez Fernández, R. Fernández Montero. C. S. Consultorio S. O. E.—P. Merino del Castillo. La Coruña: C. S. Padron—J. M. López Abuín; C. S. Muros—G. López Méndez; C. S. Ribeira—J. Torres Colomer; C. S. Conxo—A. Suarez Domínguez; C. S. Fontiñas—C. Freiria Tato; C. S. Rianxo—J. A. Santos Rodríguez; C. S. A. Pobra Do Caramiñal—M. Pérez Llamas; C. S. Boiro—L. Vaamonde Monsquera; C. S. Calo—J. M. Pérez Crespo; C. S. Noia—J. R. Girón Daviña. La Rioja: C. S. Calahorra—C. Vera López, J. J. Antoñanzas Quiñones; C. S. Alfaro—J. M. Orive Abos. Logroño: C. S. Espartero—A. Jiménez de Miguel; C. S. Joaquín Elizalde—G. Navascués Beltrán. León: C. S. Fabero—E. Gonzalez Berjon; C. S. de Astorga—C. Vázquez Rojo; C. S. Jose Aguado—R. Pérez Cubero; C. S. Mansilla de las Mulas—M. L. Gallego Velázquez; C. S. Jose Aguado—J. L. Pérez Laiz, C. Onrubia Baticón; C. S. Santa María del Páramo—L. García Burriel, J. Mosquera Ramos; C. S. de Bembibre—G. Fernández Nuñez. Madrid: C. S. Bustarviejo—G. Anton Martín; C. S. Finisterre—E. Moreno González; C. S. Fuencarral—J. L. Martínez Carrasco; C. S. Periodistas—R. Alvarez Cáceres; C. S. Chopera—J. J. González Marcos; C. S. Barrio del

Aeropuerto—A. Herranz Chaves; Clínica Rioja—A. Pretel García; C. S. Castillo de Uclés—D. Ly Pen; c/Castillo de Simancas 12—Y. López Arienza; S. O. E. San Francisco de Paula—I. Hortelano Galán, A. Leal García, I. González García; S. O. E. Santurce—J. Galindo Piqueras; S. O. E. Virgen de Africa—A. Polo Ampuero; C. S. Manzanares del Real—A. Alonso Babarro; Ramonet 12—L. Romero Garrido; C. S. Dr Luengo—V. Arenas González, P. Romero Marquez, E. Muniz Domínguez; C. S. Coronels de Palma—F. Martín Castillo; C. S. Gregorio Marañón—J. C. Cabello Rodenas, A. Bravo Malo, M. Martínez Abad; C. S. Dr Granero—M. C. Cardesa Sabio; Residencia de la Comunidad de Aranjuez—A. Ruiz Ríos; C. S. Aranjuez—L. de la Fuente Martín, J. Caballer Rodilla; C. S. Valdemoro—M. Martín Vidales; C. S. Navalcarnero—A. Gómez Fernández; C. S. Andres Mellado—C. Albuquerque Sacristan, J. Pastor Viejo-Bueno; Ambulatorio Avda. Portugal—M. P. de Miguel Novoa; C. S. Valdezarza—A. Riba Soto; C. S. Boadilla—A. Pintado King; Res. Geriatrica S. Luis Gonzaga—J. A. Cabeza Ramis; Res. Geriatrica de la Com. Las Rozas—J. Moreno del Prado; C. S. Villalba—V. Baos Vicente; C. S. Argüelles—J. Carreira Delgado; C. S. Majadahonda—M. Ramírez Ariza; C. S. Aravaca—L. Martínez Socias; C. S. Las Rozas—A. Moron Alejandro; C. S. Guadarrama—M. A. Herrero Olivares; C. S. Becerril—F. Blázquez González; C. S. Villalba—A. García Ontiveros; C. S. Navacerrada—S. Martín Martín; C. S. Carmen Calzado—A. Alonso Méndez; C. S. Reyes Magos—M. Robres Oriete; C. S. Manuel Merino—F. García Areces; C. S. La Plata—M. Palacios Romero; C. S. Alcalde Bartolome—J. Aparicio Velasco; C. S. Felipe-II—M. A. Miramon, C. Codorni Insausti; C. S. Azorín—A. García Sánchez; C. S. Alcalde Bartolome—D. Lagares Serrano. Malaga: C. S. El Palo—J. C. López Peral; Consultorio Cuevas de San Marcos—J. Alcántara Montiel; Centro Salud El Palo—J. Barceló Aguilar; Consultorio La Cala del Moral—J. M. Cabras Dueñas; Ambulatorio Bailen—J. M. Palomas Bueno; C. S. Fuengirola Este—A. Canales Rodríguez, J. C. Velasco Ortega; Serv. Médico Policia Nacional—J. A. Rodríguez Cruzado; Consultorio S. A. S.—J. J. Pérez Méndez; C. S. Estepona—J. L. Carrasco Martín; C. S. Carranque—J. C. Bravo Navas, C. Rodríguez Cortés; C. S. Ciudad Jardín—G. Prats López, A. Jiménez Sánchez; C. S. Rincón de la Victoria—A. Grndona Mayayo. Navarra: Consultorio Ablitas—F. Fdez Botana; C. S. Corella—I. Villanueva Gómez; C. S. Allo—G. Aramendia Bergaraetxea. Palencia: C. S. Carrión de los Condes—F. Marcos Fernández. Segovia: C. S. Nava Asuncion—J. Castro Bocos; C. S. Fuencisla—J. Rodriguez Sanz. Toledo: Consultorio Villaseca de la Sagra—A. Gómez Alemany; C. S. Polígono—R. López Serrano; Consultorio Dr Oliva—F. Jose Oliva Gómez; Consultorio de Galvez—A. Prieto Perea, A. Fernández-Pro Ledesma. Valladolid: C. S. Rondilla 2—J. Carton Trigo; C. S. Zaratan—Jose M. Bravo Trigo; C. S. Parquesol—T. Moran Caballero. Vitoria: C. S. Arambizkarra I—T. Villanueva Irazabal; C. S. Zumakera—M. M. Marco Pérez; C. S. Central 3^a—M. Salazar Lázaro; C. S. La Habana—A. López de Ocáriz.