

Association between refractory hypertension and cardiometabolic risk. The HIPERFRE study

F. Otero Raviña¹, L. Grigorian Shamagian², M. Lado López³, Á. Lado Llerena⁴, V. Turrado Turrado⁵, J. A. Santos Rodríguez⁵, C. Pazo Paniagua⁶, J. A. Vázquez Mallo⁷, L. Vaamonde Mosquera⁸, J. R. González Juanatey² and Grupo Barbanza

¹Sección Coordinación Asistencial. Servizo Galego de Saúde. Santiago de Compostela. ²Servicio de Cardiología. Hospital Clínico Universitario de Santiago de Compostela. ³Centro de Salud de Ribeira. ⁴Centro de Salud de Outes. ⁵Centro de Salud de Rianxo. ⁶Ambulatorio Concepción Arenal de Santiago de Compostela. ⁷Centro de Salud de Arteixo. ⁸Centro de Salud de Boiro.

Nefrología 2008; 28 (4) 425-432

SUMMARY

Background and Aim: Resistant hypertension (R-HT) is defined by the presence of uncontrolled blood pressure in patients treated with three or more drugs, being one of them diuretic. We sought to evaluate the prevalence and features of patients with R-HT attended at Primary Care of our environment.

Method: 1,724 hypertensive patients attended by 35 physicians at 14 Primary Care Units were analyzed in this descriptive, transversal, multicentral study.

Results: Patients (41.5% males) with a mean age of 67 ± 11 years, being half of them obese. Blood pressure is controlled in 41.6% and the prevalence of R-HT is of 13.2%. This latter group of patients is characterized by an older age (69 vs 67 years, $p < 0.01$) and more frequent obesity (62% vs 43%, $p < 0.001$), diabetes (55% vs 11%, $p < 0.001$), hyperlipidemia (68% vs 59%, $p < 0.05$), and metabolic syndrome (68% vs 22%, $p < 0.001$). At least half of them present some kind of end-organ damage. No pharmacological treatment is prescribed to 3% of these patients and 37% of them are on monotherapy. There is a higher prescription of angiotensin receptor, calcium channel, beta and alpha-blockers in the group of patients with R-HT. There is an independent and direct relationship between R-HT and age, male gender, diabetes, obesity, metabolic syndrome, and an inverse relationship with ischemic cardiopathy.

Conclusions: The prevalence of R-HT at Primary Care Units is of 13% and is related with age, male gender and metabolic risk factors.

Key words: Blood pressure. Resistant hypertension. Primary Care. Prevalence. Treatment.

RESUMEN

Fundamento y objetivo: Se define como hipertensión arterial refractaria (HTA-R) la persistencia del mal control de la presión en pacientes tratados con tres o más fármacos, incluyendo un diurético. Pretendemos estimar la prevalencia

y las características de pacientes con HTA-R en el ámbito de la Atención Primaria en nuestro medio.

Metodología: Estudio descriptivo, transversal y multicéntrico, en el que participaron 35 médicos de 14 Centros de Salud, registrando las características de 1.724 hipertensos. **Resultados:** Pacientes (41,5% varones) con edad media de 67 ± 11 años; la mitad, obesos. El 41,6% tienen la presión controlada y la prevalencia de HTA-R es del 13,2%. En este grupo la edad media es significativamente mayor (69 vs 67 años, $p < 0,01$) y son más frecuentes la obesidad (62% vs 43%, $p < 0,001$), la diabetes (55% vs 11%, $p < 0,001$), la dislipemia (68% vs 59%, $p < 0,05$) y el síndrome metabólico (68% vs 22%, $p < 0,001$). En la mitad de los pacientes hay afectación de algún órgano diana. El 3% de los pacientes no recibe tratamiento farmacológico y el 37% está con monoterapia. En el grupo de HTA-R hay mayor prescripción de ARA-II, antagonistas del calcio, bloqueadores beta y bloqueadores alfa. La HTA-R se asocia de forma independiente y directamente con la edad, el sexo masculino, la presencia de diabetes, obesidad y síndrome metabólico, e inversamente con la presencia de cardiopatía isquémica.

Conclusiones: La HTA-R en el ámbito de la Atención Primaria tiene una prevalencia del 13% y se asocia con la edad, el sexo masculino y los factores de riesgo metabólicos.

Palabras clave: Presión arterial. Hipertensión refractaria. Atención Primaria. Prevalencia. Tratamiento.

INTRODUCTION

Arterial hypertension (AHT) represents the main determinant of cardiovascular disease in Spain.^{1,2} Various studies conducted in recent years show that this cardiovascular risk factor is the leading cause of overall and cardiovascular mortality, and also of cardiovascular and renal complications.^{3,6} It should be noted that more than 50% of patients with clinical cardiovascular disease (ischemic heart disease, atrial fibrillation, heart failure, stroke, peripheral artery disease, nephropathy, etc.) have a history of AHT.⁷

Both from the viewpoints of primary and secondary prevention, i.e. in the whole continuum of cardiovascular risk in hypertensive patients, blood pressure control has been shown

Correspondence: Fernando Otero-Raviña
Servicio Galego de Saúde
Edif. Admvo. San Lázaro
Santiago de Compostela
15771 A Coruña. España
fernando.otero.ravina@serga.es

to prolong life and to reduce the risk of complications.^{5,8-11} Moreover, clinical practice guidelines state that goal pressure varies depending on the risk of patients.^{2,12-14}

In standard clinical practice, pressure control is far from what could be considered adequate. While this is highly variable depending on the study setting, in conditions associated to AHT it is uncommon, even in large clinical trials, to see pressure control rates higher than 40% of the study population.^{7,15-18}

Multiple factors may account for a poor blood pressure control in clinical practice. Most common factors include poor patient compliance, use of inadequate antihypertensive strategies including no medication changes when the physician in charge detects a poor pressure control, non-synergistic drug combinations, inadequate dosage, and so on. These are elements that should be taken into account when designing strategies intended to improve the extent of blood pressure control in any group of hypertensive patients.^{6,17,19-22}

Refractory hypertension (R-HT), defined by the guidelines as a persistent poor control of blood pressure in patients treated with at least three drugs, including a diuretic,¹³ is a clinical condition that has been shown to be closely related to prognosis and has a poorly known prevalence, variable depending on the populations analyzed and the characteristics of its studies.²³⁻²⁵ Presence of R-HT requires that secondary arterial hypertension is ruled out, as well as performance of a series of supplemental tests and implementation of changes in the therapeutic strategy intended to better assess cardiovascular and renal involvement and to try and optimize the degree of control.^{26,27}

The HIPERFRE study (Refractory arterial hypertension and renal function) was intended to estimate R-HT prevalence and the clinical and therapeutic characteristics of patients with R-HT in a primary care setting.

PATIENTS AND METHODS

Study protocol

Thirty-five primary care physicians from 14 healthcare centers in the southwestern area of the province of A Coruña

(Spain) participated as investigators in this multicenter, cross/sectional, descriptive study. Each investigator enrolled, in the first quarter of 2006, up to 50 patients attending his/her office who met the previously established inclusion criteria: patients older than 18 years diagnosed of AHT and giving express consent to participate in the study. A total of 6,431 patients had to be screened to achieve 2059 eligible patients (32%, hypertensive patients over 18 years of age), of whom 1,750 (85%) gave their consent to participate. The information collected was subject to an internal audit to assure its quality. This audit found that 26 patients were not valid for statistical analysis because of missing data, and the final sample analyzed therefore consisted of 1,724 patients.

Variables analyzed

All patients enrolled into the study were performed a clinical history, physical examination, and electrocardiographic and biochemical controls. Their main demographic and clinical characteristics were recorded, as well as the treatment prescribed.

The recorded blood pressure measurement was taken on the recruitment day using a calibrated and revised sphygmomanometer. All measurements were taken in all centers using the same procedure: with the patient sitting and after at least a 5-minute rest, two measurements were taken with a 5-minute interval, and the mean value was calculated. Controlled AHT was defined as BP values under 140/90 mm Hg, except in diabetic patients, in whom the corresponding values were 130/80 mm Hg.¹³

All patients with a body mass index of 30 kg/m² of higher were considered obese. Diagnosis of left ventricular hypertrophy was made by investigators based on Sokolow-Lyon (sum of S wave in lead V1 and R wave in leads V5 or V6 greater than 35 mm) and/or Cornell electrocardiographic criteria (sum of R wave in lead aVL and S wave in lead V3 greater than 28 mm in males or 20 mm in females). The ATP III criteria²⁸ were used to diagnose metabolic syndrome, and renal failure was defined as a glomerular filtration rate under 60 mL/min, as estimated by the Cockcroft and Gault formula.

Table I. General characteristics of patients enrolled into the HIPERFRE study. Sex distribution

	Total 1,724 (100%)	Males 716 (41.5%)	Females 1,008 (58.5%)	P
Age (\bar{X} , years)	67.4 ± 11.4	66.4 ± 11.5	68.1 ± 11.3	< 0.01
Weight (\bar{X} , kg)	77.7 ± 13.9	83.8 ± 13.9	73.4 ± 12.3	< 0.001
Height (\bar{X} , cm)	159.7 ± 8.7	166.6 ± 6.8	154.7 ± 6.3	< 0.001
Abd circ (\bar{X} , cm)	98.6 ± 12.9	101.4 ± 12.2	96.5 ± 12.9	< 0.001
BMI (kg/m ²)				
\bar{X}	30.4 ± 4.7	30.2 ± 4.4	30.7 ± 4.8	< 0.05
< 20	2 (0.1)	1 (0.1)	1 (0.1)	} < 0.05
20-25	169 (9.8)	68 (9.5)	102 (10.1)	
25-30	686 (39.8)	304 (42.5)	382 (37.9)	
> 30	867 (50.3)	343 (47.9)	523 (51.9)	
Systolic BP (mmHg)	139.0 ± 16.4	137.6 ± 16.3	140.0 ± 16.5	< 0.01
Diastolic BP (mmHg)	80.0 ± 9.6	79.3 ± 10.5	80.4 ± 9.0	< 0.05
BP control	717 (41.6)	290 (40.5)	427 (42.4)	ns

Abd circ: abdominal circumference. BMI: body mass index. BP: blood pressure. ns: non statistically significant difference.

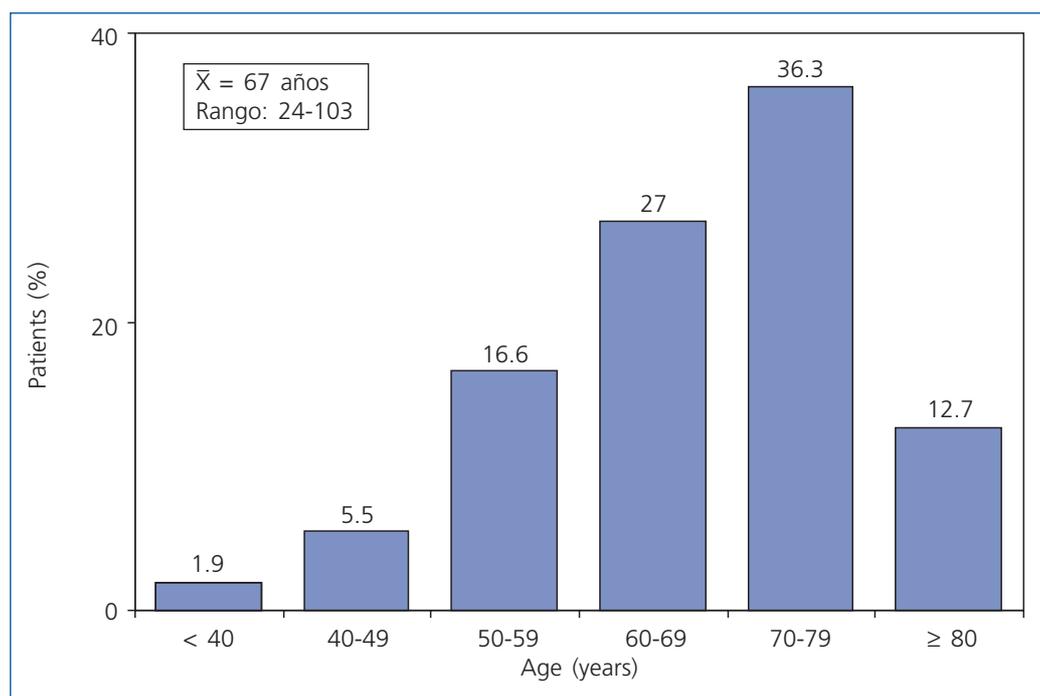


Figure 1. Patients enrolled into the HIPERFRE. Age group distribution.

Statistical analysis

Results of qualitative variables are given as absolute frequencies and percentages, while results of quantitative variables are given as mean \pm standard deviation. A descriptive statistical analysis based on frequency tables of categorical variables was performed, using a Pearson's Chi-square test, to test the significance of the association between qualitative variables. A Student's t test for independent samples was used to compare means between groups. A Pearson's correlation test was used to find the correlation between clinical variables and the groups of patients with controlled, uncontrolled, and refractory AHT.

In order to detect the factors independently related to uncontrolled AHT and R-HT, taking as reference the group with controlled AHT, a multinomial logistic regression model was constructed, whose results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). This model included the following variables: age (ongoing), sex, diabetes, dyslipidemia, smoking, alcoholism, obesity, metabolic syndrome, left ventricular hypertrophy, ischemic heart disease, myocardial revascularization, heart failure, syncope, pacemaker, atrial fibrillation, valve disease, cerebrovascular disease, peripheral vascular disease, and renal failure.

Statistical data processing was performed using software SPSS 14.0 for Windows. Differences with a probability of type I error less than 5% were considered statistically significant.

RESULTS

Table I summarizes the characteristics of the 1,724 hypertensive patients analyzed, of whom 41.5% were males. Mean age was 67 ± 11 years, with females being significantly older. Forty-nine percent of patients were older than 70 years (fig.

1). Half the study patients were obese, and mean body mass index was 30.4 kg/m^2 .

Blood pressure was controlled in 41.6% of patients, and 34.9% of all patients required less than three drugs. No significant sex- or age-related differences were seen in blood pressure control. Among the remaining patients in whom therapeutic BP goals were not reached, 228 were taking three or more antihypertensive drugs, including a diuretic. Prevalence of R-HT was therefore 13.2% (95% CI, 11.6-14.8), while the remaining 45.2% not taking the drugs required to meet refractoriness criteria formed the group of uncontrolled hypertensive patients (fig. 2). Prevalence of isolated systolic hypertension was 25.5% (95% CI, 24.5%-26.5%).

Table 2 shows the characteristics and risk factors of patients, distributed among the three groups established based on blood pressure control: controlled, uncontrolled, and refractory hypertensive patients. Diabetes, dyslipidemia, alcoholism, obesity, and metabolic syndrome were more common in the R-HT group.

Target organ involvement was found in half the patients, mainly renal failure. Thirty-seven percent of patients had a glomerular filtration rate under 60 mL/min (table II). However, if the five grades of failure are considered, 85% of patients had renal involvement (grade I, 3.4%; grade II, 45.0%; grade III, 34.8%; grade IV, 1.7%). In addition, 13.3% of patients had microalbuminuria (30-300 mg/g of creatinine) and 2.0% macroalbuminuria, with a median of 10 mg/g and an interquartile range of 6-19 mg/g for all patients.

As regards treatment, only 50 patients (2.9%) were not receiving drug treatment. Dietary measures and physical exercise had been prescribed to these patients, but blood pressure control had only been achieved in 36% of them. All other patients were taking any of the drugs listed in Table IV, either as monotherapy (37%) or in combination with other antihyper-

Table II. Characteristics of patients enrolled into the HIPERFRE study. Distribution by blood pressure control

	Total 1,724 (100%)	C-HT 717 (41.6%)	UC-HT 779 (45.2%)	R-HT 228 (13.2)	r	p
Age	67.4 ± 11.4	67.2 ± 11.9	67.1 ± 11.1	69.3 ± 10.5	0.04	ns
Sex (M)	716 (41.5)	290 (40.4)	324 (41.6)	102 (44.7)	0.03	ns
Diabetes	497 (28.8)	75 (10.5)	297 (38.1)	125 (54.8)	0.40	< 0.001
Dyslipidemia	1,052 (61.0)	424 (59.1)	472 (60.6)	156 (68.4)	0.05	< 0.05
Smoking	141 (8.2)	58 (8.1)	70 (9.0)	13 (5.7)	-0.02	ns
Alcoholism	81 (4.7)	23 (3.2)	46 (5.9)	12 (5.3)	0.05	< 0.05
Obesity	867 (50.3)	306 (42.7)	419 (53.8)	142 (62.3)	0.14	< 0.001
Metab synd	717 (41.6)	156 (21.8)	407 (52.3)	154 (67.7)	0.35	< 0.001

C-HT: controlled arterial hypertension. UC-HT: uncontrolled arterial hypertension. R-HT: refractory arterial hypertension. M: males. Metab synd: metabolic syndrome according to ATP III criteria. r: Pearson's correlation coefficient. ns: non statistically significant difference.

tensive drugs (63%). The mean number of drugs prescribed per patient was 1.8 ± 0.9, with a median number of 2 drugs. The mean numbers of drugs in the groups of controlled, uncontrolled, and refractory patients were 1.8, 1.5, and 3.2 respectively. Table IV shows a greater prescription of angiotensin II receptor blockers (ARBs), calcium channel blockers, beta-blockers, and alpha-blockers in the R-HT group as compared to the two other groups.

A multivariate analysis showed R-HT to be independently and directly associated to age, male sex, presence of diabetes mellitus, obesity, and metabolic syndrome, and inversely associated to the presence of ischemic heart disease. AHT is in turn directly associated to diabetes, metabolic syndrome, and alcoholism, and inversely associated to ischemic heart disease, heart failure, atrial fibrillation, and valve disease. In both

cases, the strongest association was found for metabolic syndrome and diabetes (table V).

DISCUSSION

Results of the HIPERFRE study suggest a high prevalence (13%) of R-HT in the general population of hypertensives seen by primary care physicians, with a 42% overall control of blood pressure values. R-HT is independently associated to age, male sex and, particularly, metabolic factors such as obesity, diabetes, and presence of metabolic syndrome. To our knowledge, this is the first study specifically analyzing the prevalence of and factors associated to R-HT in a large sample of hypertensive patients attending primary care practices in Spain. These results do not only contribute to a better un-

Table III. End-organ involvement in patients in the HIPERFRE study. Distribution by blood pressure control

	Total 1,724 (100%)	C-HT 717 (41.6%)	UC-HT 779 (45.2%)	R-HT 228 (13.2)	r	p
IHD	203 (11.8)	111 (15.5)	67 (8.7)	25 (11.0)	-0.07	< 0.01
CHF	79 (4.6)	47 (6.6)	14 (1.8)	18 (7.9)	-0.03	ns
PVD	127 (7.4)	48 (6.7)	60 (7.7)	19 (8.3)	0.02	ns
CVD	108 (6.3)	54 (7.5)	41 (5.3)	13 (5.7)	-0.04	ns
RF	629 (36.5)	285 (39.8)	268 (34.5)	76 (33.3)	-0.05	< 0.05
EOI	850 (49.3)	397 (55.3)	344 (44.2)	109 (47.8)	-0.08	< 0.01

C-HT: controlled arterial hypertension. UC-HT: uncontrolled arterial hypertension. R-HT: refractory arterial hypertension. IHD: ischemic heart disease. CHF: congestive heart failure. PVD: peripheral vascular disease. CVD: cerebrovascular disease. RF: renal failure (glomerular filtration rate under 60 mL/min, as estimated by the Cockcroft and Gault formula). EOI: end-organ involvement (at least one of the previous events). r: Pearson's correlation coefficient. ns: non statistically significant difference.

Table IV. Treatment prescribed to patients enrolled into the HIPERFRE study. Distribution by blood pressure control

	Total 1,724 (100%)	C-HT 717 (41.6%)	UC-HT 779 (45.2%)	R-HT 228 (13.2)	r	P
Diuretics	896 (52.0)	347 (48.4)	321 (41.2)	228 (100)	0.23	< 0.001
Antialdost	28 (1.6)	14 (2.0)	3 (0.4)	11 (4.8)	0.03	ns
ACEIs	577 (33.5)	240 (33.5)	265 (34.0)	72 (31.6)	-0.01	ns
ARBs	853 (49.5)	343 (47.8)	360 (46.2)	150 (65.8)	0.08	< 0.01
CCBs	428 (24.8)	158 (22.0)	129 (16.6)	141 (61.8)	0.21	< 0.001
β -blockers	301 (17.5)	144 (20.1)	77 (9.9)	80 (35.1)	0.05	< 0.05
α -blockers	75 (4.4)	22 (3.1)	13 (1.7)	40 (17.5)	0.16	< 0.001

C-HT: controlled arterial hypertension. UC-HT: uncontrolled arterial hypertension. R-HT: refractory arterial hypertension. ACEIs: angiotensin converting enzyme inhibitors. ARBs: angiotensin II receptor blockers. r: Pearson's correlation coefficient. ns: non statistically significant difference.

derstanding of the situation of AHT in our setting, but also provide new hypotheses for developing strategies aimed at improving the management of patients with R-HT.

Prevalence and clinical characteristics of patients with R-HT

Little epidemiological and clinical information is available about the prevalence and clinical characteristics of patients with R-HT. An overall prevalence of approximately 10%, that increases to more than 20% in specialized units from tertiary hospitals, has been reported, but the information available in

Spain is usually limited to studies on small numbers of patients in which, in addition to documenting the clinical refractory status, an analysis was made of some related clinical aspects.²³⁻²⁵

Various aspects should be considered when analyzing the results of this study. The existence of a pseudoresistance phenomenon related to a «white coat effect» or to an inadequate procedure for measuring blood pressure may overestimate the prevalence of R-HT.²⁹ In this regard, ambulatory blood pressure monitoring (ABPM) may help identify hypertensive patients with a normal behavior during the activity-sleep cycle, and provide also useful information for risk stratification of

Table V. Factors associated to uncontrolled and refractory hypertension in the HIPERFRE study. Multivariate analysis

	Uncontrolled AHT			Refractory HT		
	OR	95% CI	p	OR	95% CI	p
Age (each year)	1.01	0.99-1.02	ns	1.03	1.01-1.05	< 0.01
Male sex	1.30	0.99-1.70	ns	1.62	1.10-2.37	< 0.05
Diabetes	4.39	3.18-6.05	< 0.001	6.34	4.24-9.50	< 0.001
Alcoholism	1.96	1.05-3.66	< 0.05	2.00	0.83-4.81	ns
Obesity	1.22	0.95-1.57	ns	1.51	1.04-2.19	< 0.05
Metabolic synd	2.85	2.17-3.74	< 0.001	4.36	2.95-6.45	< 0.001
Ischemic heart dis	0.58	0.39-0.88	< 0.05	0.40	0.21-0.73	< 0.01
Heart failure	0.26	0.12-0.55	< 0.001	0.78	0.37-1.65	ns
Atrial fibrillation	0.44	0.26-0.75	< 0.01	1.42	0.26-0.75	ns
Valve disease	0.38	0.20-0.72	< 0.01	0.84	0.40-1.78	ns

AHT: arterial hypertension. OR: odds ratio. CI: confidence interval. ns: non statistically significant difference. The reference category is controlled arterial hypertension.

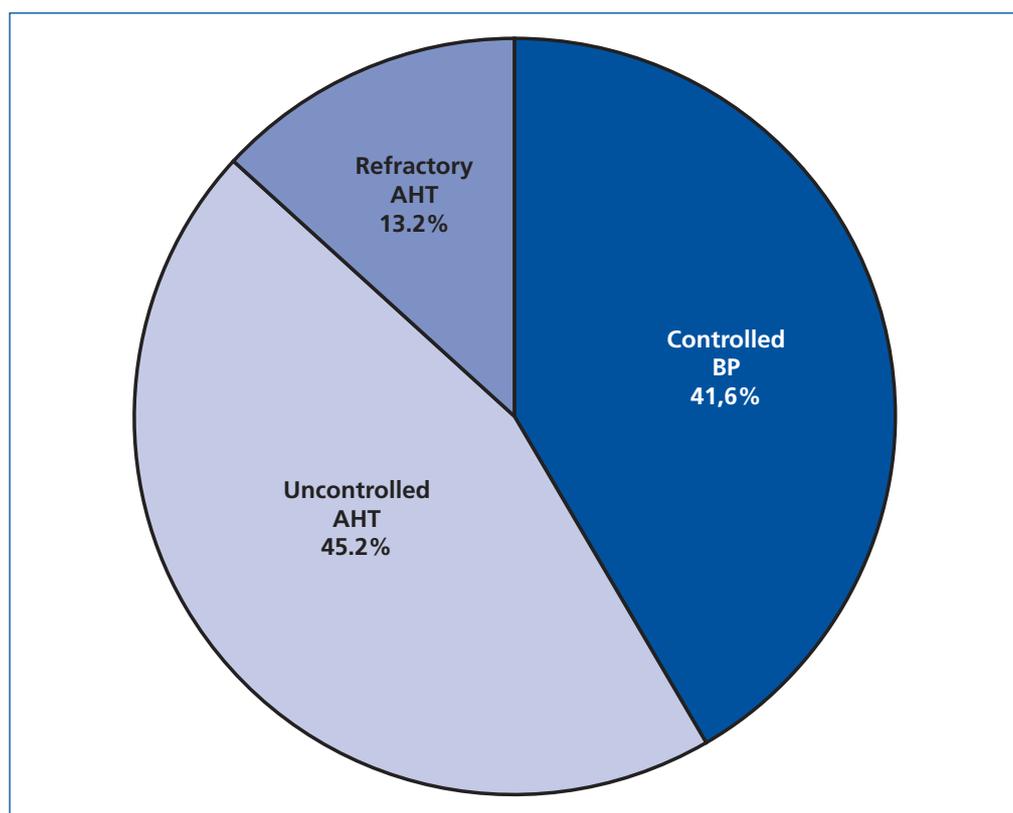


Figure 2. Blood pressure control. Prevalence of refractory hypertension in patients in the HIPERFRE study. AHT: arterial hypertension. BP: blood pressure.

these patients, as only the group with R-HT and an abnormal behavior during monitoring has a significantly increased cardiovascular risk,³⁰ in contrast to the group diagnosed of R-HT by a casual blood pressure measurement but having a normal ABPM.

All hypertensive patients, but particularly the group of patients with R-HT, should undergo a complete clinical evaluation including supplemental tests to assess cardiac, vascular, and renal involvement. Causes of secondary AHT and factors that may contribute to an inadequate treatment response should also be identified. According to our study results, the proportion of patients in whom primary care physicians should perform such evaluation is relatively important. Evaluation will preferentially include a careful analysis of treatment compliance, adequate dosage of antihypertensive drugs, and even, in line with current recommendations by clinical practice guidelines,¹³ an ABPM.

Metabolic cardiovascular risk factors in R-HT

In addition to analysis of the prevalence in a large sample of hypertensive patients, aggregation of metabolic risk factors with R-HT is one of the main findings from the HIPERFRE study. In the multivariate analysis of factors showing a significant independent association to the refractory status deserve particular mention, in addition to age and male sex, diagnoses of diabetes mellitus, obesity, and metabolic syndrome. Over 60% of patients with R-HT were obese (BMI > 30) and had metabolic syndrome, and more than 50% had diabetes.

These findings suggest that different components of cardiovascular risk are aggregated in the same patient because they probably share common pathogenetic mechanisms and, based on our study results, insulin resistance could be one of the elements relating obesity, metabolic syndrome, diabetes, and R-HT. Insulin resistance causes a hyperinsulinemia state that has been shown to be associated to mechanisms causing blood pressure increase, and thus greater difficulties for blood pressure control. Sodium retention, activation of sympathetic nervous system, altered transmembrane ion transport, proliferation of smooth muscle fibers, and prostaglandin metabolism disorders are mechanisms dependent on hyperinsulinism and associated to AHT.³¹

Various studies have shown that blockade of the renin-angiotensin-aldosterone system with angiotensin converting enzyme inhibitors (ACEIs) and ARBs has a similar antihypertensive efficacy, but is also associated to an improved carbohydrate metabolism, with a reduction in cases of *de novo* diabetes.³² Multiple mechanisms that could account for this effect have been described. ACEIs could improve glucose utilization by cells through the actions of bradykinin and nitric oxide,³³ and ARBs through the insulin signalling pathway, enhancing by various mechanisms the availability of channels for glucose utilization by cells.³⁴

Thus, after an adequate clinical evaluation, the therapeutic strategy in obese and diabetic patients with R-HT should include, in addition to lifestyle changes and an adequate management of hyperglycemia, an ACEI or ARB at the maximum recommended doses.

Implications and limitations

While this was a cross-sectional clinical and epidemiological study that did not allow for measuring the impact of R-HT on prognosis, we think the study reflects its real situation in our environment in the larger patient sample reported to date. In addition, the study allows for proposing strategies for a better clinical evaluation and therapeutic approach in this patient group.

While limitations of casual blood pressure measurement and the value of ABPM for clinical evaluation of patients with R-HT are known, the study methods, particularly the conditions for blood pressure measurement, represent an element of quality of the information reported.

CONCLUSIONS

A high prevalence of R-HT is found in the population of hypertensive patients attending primary care practices. A significant proportion of uncontrolled hypertensive patients do not meet refractoriness criteria because they do not meet the therapeutic conditions required for definition of R-HT. We think that association of R-HT with metabolic risk factors, with insulin resistance as a common pathogenetic component, provides new possibilities for intervention and research in a relevant clinical condition with a high cardiovascular and renal risk.

REFERENCES

- Banegas Banegas JR. Epidemiología de la hipertensión arterial en España. Situación actual y perspectivas. *Hipertensión* 2005; 22: 353-62.
- Marín R, De la Sierra A, Armario P, Campo C, Banegas JR, Gorostidi M. Guía sobre el diagnóstico y tratamiento de la hipertensión arterial en España 2005. *Med Clin (Barc)* 2005; 125: 24-34.
- Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA y cols. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990; 335: 827-38.
- Banegas Banegas JR, Rodríguez-Artalejo F, De la Cruz Troca JJ, De Andrés Manzano B, Del Rey Calero J. Mortalidad relacionada con la hipertensión y la presión arterial en España. *Med Clin (Barc)* 1999; 112: 489-94.
- Weber MA. Hypertension treatment and implications of recent cardiovascular outcome trials. *J Hypertens Suppl* 2006; 24: S37-44.
- Márquez Contreras E, Coca A, De la Figuera von Wichmann M, División JA, Llisterri JL, Sobrino J y cols. Perfil de riesgo cardiovascular de los pacientes con hipertensión arterial no controlada. Estudio Control-Project. *Med Clin (Barc)* 2007; 128: 86-91.
- González-Juanatey JR, Alegría Ezquerro E, Lozano Vidal JV, Llisterri Caro JL, García Acuña JM, González Maqueda I. Impacto de la hipertensión en las cardiopatías en España. Estudio Cardiotens 1999. *Rev Esp Cardiol* 2001; 54: 139-49.
- Julius S, Kjeldsen S, Weber M, Brunner HR, Ekman S, Hansson L y cols. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; 363: 2022-31.
- Weber MA, Julius S, Kjeldsen SE, Brunner HR, Ekman S, Hansson L y cols. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE trial. *Lancet* 2004; 363: 2049-51.
- Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; 362: 1527-35.
- González-Juanatey JR, Conthe P. Enfermedad cardiovascular y cardiopatía hipertensiva. Más allá del corazón. *Rev Esp Cardiol* 2006; 126: 99-100.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr y cols. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560-72.
- Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G y cols. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007; 28: 1462-536.
- Giles TD. Should we redefine hypertension? *Curr Cardiol Rep* 2006; 8: 395-8.
- Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH y cols. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens (Greenwich)* 2002; 4: 393-404.
- Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR y cols. Hypertension treatment and control in five European countries, Canada and the United States. *Hypertension* 2004; 43: 10-7.
- Llisterri Caro JL, Rodríguez Coca GC, Alonso Moreno FJ, Lou Arnal S, División Garrote JA, Santos Rodríguez JA y cols. Control de la presión arterial en la población hipertensa española atendida en Atención Primaria. Estudio PRESCAP 2002. *Med Clin (Barc)* 2004; 122: 165-71.
- Otero Raviña F, Grigorian Shamagian L, Fransi Galiana L, Názara Otero C, Fernández Villaverde JM, González Juanatey JR y cols. Estudio gallego de insuficiencia cardíaca en atención primaria (estudio GALICAP). *Rev Esp Cardiol* 2007; 60: 373-83.
- Márquez Contreras E, Gil Guillén V, Casado Martínez JJ, Martel Claros N, De la Figuera von Wichmann M, Martín de Pablos JL y cols. Análisis de los estudios publicados sobre el incumplimiento terapéutico en el tratamiento de la hipertensión arterial en España entre los años 1984 y 2005. *Aten Primaria* 2006; 38: 325-32.
- Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure and low density lipoprotein cholesterol: a randomized controlled trial. *JAMA* 2006; 296: 2563-71.
- Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. *Am J Hypertens* 2006; 19: 1190-6.
- Mazón Ramos P, Bertomeu Martínez V, Palma Gámiz JL, Quiles Granada J, Guindo-Soldevilla J, González-Juanatey JR. Tratamiento global del riesgo cardiovascular en el paciente hipertenso. *Rev Esp Cardiol* 2007; 60 Supl. 1: 79-91.
- Alderman MH, Budner N, Cohen H, Lampion B, Ooi WL. Prevalence of drug resistant hypertension. *Hypertension* 1988; 11: II 71-5.
- Yakovlevitch M, Black HR. Resistant hypertension in a tertiary care clinic. *Arch Intern Med* 1991; 151: 1786-92.
- González Benítez MA; Fernández Sánchez ML, Fernández Parrilla R, Beltrán Robles M, Ramos Guerrero AJ, Jarast Olivari D y cols. Hipertensión arterial refractaria verdadera. Estudio de prevalencia en una consulta hospitalaria. *Hipertensión* 2005; 22: 189-94.
- Epstein M. Resistant hypertension: prevalence and evolving concepts. *J Clin Hypertens (Greenwich)* 2007; 9: 2-6.
- Park J, Campese V. Clinical characteristics of resistant hypertension: the importance of compliance and the role of diagnostic evaluation in delineating pathogenesis. *J Clin Hypertens (Greenwich)* 2007; 9: 7-12.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486-97.
- Sierra C, De la Sierra A, Sobrino J, Segura J, Banegas JR, Gorostidi M y cols. Monitorización ambulatoria de la presión arterial (MAP): características clínicas de 31.530 pacientes. *Med Clin (Barc)* 2007; 129: 1-5.

30. Redón J, Campos C, Narciso ML, Rodicio JL, Pascual JM, Ruilope LM. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension* 1998; 31: 712-8.
31. Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. *Endocr Rev* 2007; 28: 463-91.
32. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007; 369: 201-7.
33. Shiuchi T, Cui TX, Wu L, Nakagami H, Takeda-Matsubara Y, Iwai M y cols. ACE inhibitor improves insulin resistance in diabetic mouse via bradykinin and NO. *Hypertension* 2002; 40: 329-34.
34. Motley ED, Eguchi K, Gardner C, Hicks AL, Reynolds CM, Frank GD y cols. Insuline-induced Akt activation is inhibited by angiotensin II in the vasculature through protein kinase C-alpha. *Hypertension* 2003; 41: 775-80.