Introduction and objectives. The aim of this study was to evaluate the use of spironolactone and doxazosin as treatment for patients with resistant hypertension.

Methods. This retrospective study involved 181 outpatients with resistant hypertension (defined as a failure of blood pressure [BP] control despite treatment with 3 drugs, one of which was a diuretic) who received additional spironolactone (n=88) or doxazosin (n=93).

Results. Mean systolic BP in the spironolactone group fell by 28 mm Hg (95% confidence interval [CI], 24-32 mm Hg; P<.001) and mean diastolic BP fell by 12 mm Hg (95% CI, 9-14 mm Hg; P<.001). The corresponding falls in the doxazosin group were 16 mm Hg (95% CI, 13-20 mm Hg; P<.001) and 7 mm Hg (95% CI, 5-9; P<.001), respectively. The decrease was significantly greater with spironolactone for both systolic (P<.001) and diastolic (P=.003) pressures. At the end of follow-up, 30% of all patients had achieved BP control, with control being more frequent with spironolactone (39%) than doxazosin (23%; P<.02). Multivariate logistic regression analysis showed that the only factors that significantly influenced the achievement of BP control were diabetes (OR, 0.17; 95% CI, 0.08-0.39; P<.001) and baseline systolic BP <165 mmHg (OR, 2.56; 95% CI, 1.11-5.90; P=.03).

Conclusions. In patients with resistant hypertension, the addition of either spironolactone or doxazosin resulted in a significant decrease in BP, though the decrease appeared to be greater with spironolactone. The presence of diabetes complicated BP control.

Key words: Spironolactone. Doxazosin. Resistant hypertension. Refractory hypertension.
INTRODUCTION

High blood pressure (HBP) resistant to treatment—or refractory high blood pressure (RHBP)—is normally defined as a blood pressure (BP) constantly above 140/90 mm Hg (≥130/80 mm Hg in patients with diabetes mellitus or clinically established kidney disease) despite having made lifestyle changes and despite treatment with at least 3 drugs (one of which is a diuretic), each at the appropriate dose.1,2 The exact prevalence of this condition is not well known, and may vary from as little as 5% among non-selected patients under the care of general physicians, to 50% in certain reference units.3 Neither are there any clear guidelines on the diagnostic and therapeutic tests that should be performed when treating RHBP; no prospective studies have been undertaken that might indicate the best diagnostic and therapeutic sequence to follow for adding a third, fourth, or fifth drug in the management of patients with either uncontrolled blood pressure or RHBP.2 Nor are the opinions of experts in this area always the same.4-7 However, recent studies have indicated that spironolactone (an aldosterone antagonist) affords an additional anti-hypertension effect when used in the treatment of RHBP,8-11 and that doxazosin has a similar effect in patients with uncontrolled HBP receiving one or several drugs.12-15 The aim of the present work was to assess the use of spironolactone or doxazosin when added to conventional treatment for RHBP, to compare the possible differences in the response to these drugs in terms of different clinical and biochemical variables, and to try to identify the clinical characteristics of patients who might show a good therapeutic response to one or the other of these agents.

METHODS

This retrospective, observational study involved patients with RHBP treated at a hypertension and vascular risk unit belonging to an internal medicine department.

Patients

Study subjects were consecutive patients with HBP, treated at the same unit between March 1, 2005 and June 30, 2007, who met the following conditions: a) to be older than 18 years of age and to have a followed stable treatment regimen including lifestyle changes (low fat and low salt diet), and/or to have received pharmacological treatment for 3 months prior to the initial inclusion assessment; b) to be receiving at least 3 drugs (including a diuretic) at the appropriate clinical doses but to have a systolic blood pressure (SBP) of >140 mm Hg and/or a diastolic blood pressure (DBP) of >90 mm Hg (>130 mm Hg SBP and/or >80 mm Hg DBP in patients with diabetes); c) to show a plasma creatinine concentration of <1.6 mg/dL in men and <1.4 mg/dL in women; and d) to have contemplated the spironolactone/doxazosin treatment period, thus allowing clinical and analytical data to be recorded.

The HBP of patients measured during consultation was confirmed in all cases by home blood pressure monitoring (HBPM) or ambulatory blood pressure monitoring (ABPM). For the patients whose BP was monitored by HBPM, the values required for confirmation of inclusion were SBP>135 mm Hg and/or DBP>85 mm Hg; for those whose BP was monitored by AMBP, the values were SBP 24 h>130 mm Hg and/or DBP 24 h>80 mm Hg.

The following patients were excluded: a) those with a diagnosis of HBP secondary to any condition; b) those with serum K concentrations at the start of the study of <3.5 mmol/L or >5.5 mmol/L; c) those for whom reasonable doubt was raised regarding adherence to treatment; and d) those with a systemic disease that might interfere with the assessment of changes in the BP.

Following initial examination patients were assigned either spironolactone or doxazosin in addition to their 3 or more anti-hypertension treatments. Monitoring was undertaken until the stabilization of the BP was achieved or the need for treatment modification was apparent. The last consultation for a patient (as part of the study) was deemed to have occurred when: a) treatment was changed by adding a new drug and/or changing the dose of those being taken to control BP; or b) when BP was under control with the target values reached (SBP<140 mm Hg and DBP <90 mm Hg, or SBP<130 mm Hg and DBP<80 mmHg for patients with diabetes); these patients were assigned to mid-term follow-up with a maintenance treatment including spironolactone or doxazosin.

Clinical Examination and Methods

All subjects underwent a normal physical examination; the body weight (kg), height (cm),
and waist measurement (cm) were also recorded. Clinical BP was measured using a mercury sphygmanometer with the patient in a sitting position following a 5 min rest period, according to the indications of the British Hypertension Society.16

Analytical Tests
All patients were subjected to analytical tests. Urinary albumin excretion was determined in 24 h urine by immunonephelometry (Behring Institute). The glomerular filtration rate was estimated using a formula employing the serum creatinine values.17 Those patients who met the criteria of the National Cholesterol Educational Program-Adult Treatment Panel III (NCEP-ATP III)18 were diagnosed as having metabolic syndrome. The diagnosis of diabetes was made following the criteria of the American Diabetes Association.19

All data (epidemiological, clinical, analytical, and treatment regimen) were stored electronically, respecting current confidentiality laws. This study was performed in accordance with standards of good clinical practice, and was approved and monitored by our hospital’s research committee. All patients gave their consent to be included.

Statistical Analysis
Continuous variables were expressed as mean (standard deviation [SD]) if they followed a normal distribution, and as medians plus interquartile range (IQR) if they did not. Categorical variables were expressed as percentages. The normality of the distribution of variables was checked using the Kolmogorov-Smirnov test. Differences in the values of variables after treatment were analyzed using the Student t test for repeated measures if the distribution was normal, and the Wilcoxon test if it as not. Comparisons between groups were made using the Student t test if the variable in question showed a normal distribution; the Mann-Whitney U test was used if it did not.

The homogeneity of variances was tested using the Levene test. Proportions were compared using the χ2 test. The association between variables and a reduction in BP was analyzed via multiple regression. The multivariate odds ratio (MOR) associated with a good treatment response was determined by logistic regression. Significance was set at α=.05. All calculations were made using SPSS v. 11.0 for Windows.

RESULTS
Of the 2958 patients who received treatment at the hypertension and vascular risk unit during the study period, 687 who were being treated with 3 or more drugs yet showed poor control of BP were initially assessed. Of these, 490 were excluded, 82 because there was reasonable doubt regarding their adherence to treatment, 125 because the HBP was suspected of being secondary to another condition or because of a kidney disorder, 151 because their HBPM or ABPM was indicative of pseudohypertension, and 122 because of concomitant systemic disease and/or the taking of medication that might interfere with the assessment of changes in BP. A total of 198 patients were therefore selected, 17 of which failed to finish their treatment with spironolactone or doxazosin, or for whom there were insufficient clinical or analytical data. Thus, the final analysis included 181 patients, 88 of whom were treated with additional spironolactone and 93 with additional doxazosin (see Table 1 for the characteristics of these patients).

No difference was seen between these groups in terms of age, body mass index, waist measurement, lipid values, or blood glucose levels; neither was any difference seen in terms of the proportion of patients with metabolic syndrome, diabetes mellitus, the use of tobacco, the use of anti-hypertension drugs, nor the use of lipid lowering drugs. No differences were seen between these groups with respect to DBP or SBP, although the latter showed a trend towards being higher in the spironolactone group (P=.06). The patients who received spironolactone showed lower uric acid (6.1 [1.5] mg/dL compared to 6.7 [1.5] mg/dL; P=.01) and creatinine (0.9 [0.2] mg/dL compared to 1.1 [0.4] mg/dL; P<.001) levels, greater excretion of albumin in the urine (13 [13] mg/24 h compared to 33 [153] mg/24 h; P<.001), and a higher glomerular filtration rate (83.9 [23.4] mL/min/1.73 m2 compared to 68.7 [20.3] mL/min/1.73 m2) than did those who received doxazosin.

A total of 179 (99%) patients met the criterion for elevated SBP, 96 (53%) for elevated DBP, and 94 (52%) for both. Seventy-four patients—33 in the spironolactone group and 41 in the doxazosin group—were confirmed as suffering RHBP by ABPM; in the rest this was confirmed by HBPM.

Of the 181 final subjects, 103 (57%) received 3 anti-hypertension drugs, 65 (36%) received 4, and 13 (7%) received 5. No drug sequencing protocol was followed; the indication for each drug was determined from the clinical characteristics of each patient. The most common drug combinations involved angiotensin converting enzyme inhibitors and or angiotensin II receptor antagonists combined with a calcium antagonist and a diuretic. A trend was seen towards the greater use of thiazide diuretics and a smaller use of loop diuretics in the spironolactone group of patients (P=.06).
The addition of doxazosin was also associated with a clear reduction in BP. The SBP was reduced by a mean 16 mm Hg (95% CI, 13-20 mm Hg; P<.001), and the DBP reduced by a mean 7 mm Hg (95% CI, 5-9 mm Hg; P<.001) (Figure 1). Doxazosin treatment was associated with a reduction in urinary albumin excretion (Table 2), and with no change in uric acid, creatinine, glomerular filtration rate or serum Na or K readings. The mean dose of doxazosin used was 4 (1.3) mg; the median treatment time before the final assessment was 6 (3-12) months.

The reduction achieved in SBP was greater among the patients who received spironolactone than those who received doxazosin (P=.001); the same was seen for the DBP (P=.003). Kidney function (as reflected by the creatinine level, serum K, the
Factors Related to Reduced Blood Pressure

Multiple regression analysis showed the reduction in SBP after additional treatment to be independently associated with baseline SBP ($\beta=.6$, 95% CI, 0.4-0.9; $P<.001$), with male gender ($\beta=12.4$, 95% CI, 1.8-23; $P=.02$), age ($\beta=−.5$, 95% CI, −0.9 to −0.1; $P=.02$) and treatment with spironolactone ($P=.02$); the mean reduction seen after adjusting for these variables and for the creatinine concentration, glomerular filtration rate, glucose level and urinary albumin excretion was 8 mm Hg (95% CI, 1-14.6) greater in this group than in the doxazosin group. The reduction in DBP was only independently associated with the baseline DBP ($\beta=.5$, 95% CI, 0.3-0.7; $P=.001$) and spironolactone treatment ($P=.04$); the mean reduction adjusted for all associated variables was 3.8 mm Hg (95% CI, 0.2-7.4 mm Hg) greater in the spironolactone group than in the doxazosin group.

Control of Blood Pressure

At the end of follow-up, 61 (34%) patients had attained the target SBP and 135 (75%) the target DBP; 55 (30%) had both under control. Attainment of control was better in the spironolactone group (39%) than the doxazosin group (23%) ($P=.02$). Table 3 compares the initial characteristics of the patients who achieved good control of BP and those who did not. Those who achieved control were younger (63 [10] years compared to 67 [10] years; $P=.04$), had lower glucose levels (106 [24] mg/dL compared to 138 [71] mg/dL), and fewer suffered metabolic syndrome ($P=.03$) or diabetes ($P=.001$).

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correlated with the baseline BP value. Those patients with the highest baseline BP values benefited from the greatest reductions. However, the probability of attaining good BP control was almost twice as great in patients with a baseline SBP of <165 mm Hg. Patients with diabetes had less chance of attaining control of their blood pressure. The reduction achieved in BP was greater with spironolactone than with doxazosin. However, patients who were treated with doxazosin experienced less deterioration of their kidney function and fewer electrolyte abnormalities than those treated with spironolactone, even though patients treated with doxazosin started off with poorer mean kidney function values (Table 1). Both therapeutic options would, however, appear to be useful from a clinical point of view and help reduce BP in patients with RHBP.

**DISCUSSION**

The results of the present study show that, in a population of patients with RHPB, the addition of spironolactone or doxazosin to ongoing anti-hypertension treatment was associated with a clear reduction in the SBP and DBP; effective control of the BP was achieved in 39% of the patients who received spironolactone and in 23% of those who received doxazosin. In both treatment groups, the magnitude of the reduction in BP was mainly correlated with the baseline BP value. Those patients with the highest baseline BP values benefited from the greatest reductions. However, the probability of attaining good BP control was almost twice as great in patients with a baseline SBP of <165 mm Hg. Patients with diabetes had less chance of attaining control of their blood pressure. The reduction achieved in BP was greater with spironolactone than with doxazosin. However, patients who were treated with doxazosin experienced less deterioration of their kidney function and fewer electrolyte abnormalities than those treated with spironolactone, even though patients treated with doxazosin started off with poorer mean kidney function values (Table 1). Both therapeutic options would, however, appear to be useful from a clinical point of view and help reduce BP in patients with RHBP.

**Comparison With the Results of Previous Studies**

The present results confirm the data provided by other authors on the impact of spironolactone on BP in small groups of patients with RHPB;
The present findings indicate that adding either spironolactone or doxazosin to standard treatment with different drugs for the treatment of RHBP is useful. Although combining prior treatment with spironolactone appears to reduce the SBP and DBP and achieve better control of the BP than combining with doxazosin, the design of the present study allows no definitive conclusions to be drawn regarding the superiority of either of these drugs over the other. However, the baseline differences between the two groups treated with these drugs in terms of the SBP and kidney function variables were taken into account in multivariate analysis, and although it cannot be completely ruled out that they had no effect, the data are indicative of spironolactone achieving greater effects. Unfortunately, no factors indicating whether a patient might respond more favorably to one or the other drug were found, although the baseline SBP and diabetes were related to the result achieved in both treatment groups (directly and inversely respectively). Certainly, no differences were seen in the baseline clinical and biochemical details of patients that responded to either drug, indicating that the use of spironolactone plus doxazosin might have a role to play. Further research based on clinical trials should answer some of these questions.

It should be remembered that the use of spironolactone or doxazosin as a fourth drug in the treatment of uncontrolled HBP is only contemplated as one of several therapeutic options by European2— and particularly British22—guidelines for the treatment of HBP. Some very respected authors do not even consider these agents as drugs of choice in their therapeutic algorithms,6 highlighting the lack

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MOR indicates multivariate odds ratio; SBP, systolic blood pressure.

also confirm the results of a study made by our own group.11 Data for a large subgroup of patients in the ASCOT study have recently been published,20 the members of which were considered to have RHBP (although not all received diuretics in their drug combinations) and who received spironolactone in addition to their normal treatment. These patients experienced a mean reduction of 22 mm Hg in the SBP and of 9.5 mm Hg in their DBP, values similar to those recorded in the present work. The present results also confirm the capacity of doxazosin to reduce the BP when added to treatment. In a study of 264 patients (although among whom only 15% received more than one anti-hypertension drug), Pessina et al14 reported a mean reduction of 15 mm Hg in SBP and of 9 mm Hg in DBP—very similar to the reductions reported in the present work. Black et al,13 who studied 89 patients with uncontrolled HBP, reported that 36% of those to whose medication doxazosin was added saw their BP controlled by the end of the study. However, these were not all patients with RHBP (not all took 2 or more anti-hypertension drugs). Data regarding the efficacy of doxazosin in populations of people with severe HBP (such as that represented by the present patients) are very rare. The only study undertaken to date to include patients with RHBP (n=27) would appear to be that of Mediavilla et al,21 who reported control of HBP to be achieved in 38% of those who received doxazosin as additional medication. None of the above studies found doxazosin to be associated with changed kidney function or abnormal analytical test results, as seen in the present work. No other work comparing the efficacy of spironolactone and doxazosin in patients with RHBP appears to exist.
of consensus in this area and the need for new data regarding their clinical use.

The present results underline the greater difficulty encountered in controlling RHBP in patients with diabetes—whether spironolactone or doxazosin are used as an additional treatment. Since the target SBP and DBP values are lower in such patients, this is hardly surprising. Nonetheless, a significant reduction in BP is always beneficial in higher risk patients such as diabetics.

It is important to keep in mind the possible prevalence of occult primary hyperaldosteronism in these patients, and in general in patients with RHBP\textsuperscript{23,24}. In the present patients, and in patients with RHBP in all other studies, the possibility of secondary hypertension needs to be borne in mind—always on the basis of indicative clinical data (hypercorticism, suspicion of vasculorenal HBP etc). Yet this is not systematically taken into account\textsuperscript{3-6}; its presence, therefore, cannot be completely ruled out in published studies.

Neither spironolactone or doxazosin use is free of secondary effects. The present study was not designed to measure these since, at the beginning of the study, all patients with significant kidney disease were excluded. Further, the reduction in BP was only measured among those who actually finished the study or until their treatment had to be modified. It is therefore difficult to draw any conclusions in this respect.

Limitations

The present study is subject to a number of limitations, the main one being its retrospective nature. Further, the patients were not randomly assigned to receive spironolactone or doxazosin treatment; probable clinical bias means no conclusions can be drawn regarding which drug provides the greater benefit. However, it should be pointed out that, in a recent review of the AHA,\textsuperscript{25} there was a noticeable absence of prospective data. Naturally, prospective studies of the type required (randomized and double blind and with a similarly large number of patients with RHBP) would encounter very serious difficulties—making manifest the usefulness of retrospective studies such as the present. Certainly, ethical problems would prevent a placebo-controlled trial in patients with RHBP. Clearly, however, the general use of these drugs can only be contemplated when controlled clinical trials involving similar patients confirm the present findings.

CONCLUSIONS

High blood pressure cannot be controlled in a large proportion of patients by lifestyle changes,\textsuperscript{26} nor even by adding pharmacological treatment.\textsuperscript{27} The present results show, however, that a reduction in BP may be possible in a significant number of patients with uncontrolled HBP or RHBP by adding spironolactone or doxazosin to their habitual treatment. Any reduction in BP is beneficial for patients with RHBP, since high BP maintained over a long period is the most important factor in the development of organic damage\textsuperscript{28} and the progression\textsuperscript{29} or regression\textsuperscript{30} of vascular damage; it is also a marker of major clinical events in patients with RHBP.\textsuperscript{31}

REFERENCES

Rodilla E et al. Spironolactone and Doxazosin Treatment in Patients With Resistant Hypertension

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