Resistant Hypertension and Mortality. An Observational Cohort Study

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ABSTRACT

Background: Resistant hypertension is characterized by elevated blood pressure (BP) despite using three antihypertensive agents. Ambulatory blood pressure monitoring (ABPM) detects the presence of white-coat resistant hypertension (24-hour BP < 130/80 mmHg). The aim of the study was to evaluate risks of death in resistant hypertension as compared to controlled hypertension, as well as in ABPM-confirmed (24-hour BP ≥130 and/or 80 mmHg), versus white-coat resistant hypertension.

Methods: We selected 8146 patients with controlled hypertension (office blood pressure < 140/90 mmHg while treated with ≤3 antihypertensive drugs), and 8577 with resistant hypertension (blood pressure ≥ 140 or ≥ 90 mmHg while treated with ≥3 drugs). All-cause and cardiovascular mortality (median follow-up 9.7 years) were compared between groups as well as between patients with white-coat (3289) and ABPM-confirmed (5288) resistant hypertension. Hazard ratios from Cox models after adjustment for clinical confounders were used for comparisons.

Results: Compared to controlled hypertension, resistant hypertension was associated with an increased risk in all-cause (hazard ratio: 1.21; 95% CI: 1.12-1.30) and cardiovascular mortality (1.33; 1.17-1.51) in confounder-adjusted models. Compared to white-coat, ABPM-confirmed resistant hypertension was associated with an increased risk of all-cause (1.45; 1.32-1.60) and cardiovascular (1.68; 1.43-1.98) mortality. When ABPM-confirmed and white-coat resistant hypertension were separately compared with controlled hypertension, only the former was associated with an increased risk of death and cardiovascular death (1.36; 1.26-1.48, and 1.56; 1.36-1.79), respectively.

Conclusion: ABPM-confirmed resistant hypertension is associated with an increased risk of death and cardiovascular death with respect to both controlled hypertension and white-coat resistant hypertension.

Keywords: ambulatory blood pressure monitoring, blood pressure, mortality, resistant hypertension, white-coat resistant hypertension

Nonstandard Abbreviations and Acronyms

ABPM: ambulatory blood pressure monitoring

ALLHAT: Antihypertensive and Lipi-Lowering Treatment to Prevent Heart Attack Trial

BMI: body mass index

DBP: diastolic blood pressure

NHANES: National Health and Nutrition Examination Survey

REGARDS: Reasons for Geographic and Racial Differences in Stroke

RH: resistant hypertension

SBP: systolic blood pressure

INTRODUCTION

Resistant hypertension (RH), defined as the inability to achieve blood pressure (BP) control with at least 3 antihypertensive drugs, one of them, preferably, a diuretic[1,2] is present in 10%-15% of the treated hypertensive population[3,4]. However, about one third of patients with RH do not have true RH because they have an exaggerated white-coat effect and exhibit normal values of 24-hour BP on ambulatory blood pressure monitoring (ABPM), and are defined as white-coat RH[4]. For this reason, most guidelines recommend the use of ABPM in patients with RH to exclude this subset from the definition of "true" RH [5-7].

Several studies have suggested an increased risk of future cardiovascular events and mortality in patients with RH[8-10]. We have shown that BP obtained through 24-hr ABPM was more informative about mortality risk than clinic or office BP[11] and this is also important in evaluating the outcome of RH patients[12-14].

Several cross-sectional analyses of the population of the Spanish ABPM Registry indicated that, first, in comparison with hypertensive patients treated and controlled with 3 or less drugs, those with RH had more frequently other cardiovascular risk factors, hypertension-mediated organ damage, and previous cardiovascular disease[15]. Second, the classification of RH in true (ABPM-confirmed) or white-coat categories, by using ABPM, also revealed important differences in the cardiovascular risk profile, with those with ABPM-confirmed RH having more cardiovascular risk factors and diseases[4].

The aim of the present study was to evaluate if these differences in the cardiovascular risk profile were translated also in differences in all-cause and cardiovascular mortality, after 10-years follow up, by comparing patients with RH and controlled hypertension, and ABPM-confirmed versus white-coat RH.

PATIENTS AND METHODS

The data that support the findings of this study are available from the corresponding authors, upon reasonable request.

Study Design

The Spanish ABPM Registry was developed to promote the use of ABPM in clinical practice. Details about recruitment characteristics have been previously reported[4,11,15]. The study was approved by the local institutional ethics committees, and informed consent was obtained from the participants. The present study is an analysis of mortality that includes 35129 treated patients who were enrolled in the registry between March 2004 and December 2014.

BP Measurements

BP was measured at the office using a validated upper-arm cuff oscillometric device, after a 5-minute rest in a sitting position. BP values were estimated as the mean of 2 readings. Thereafter, 24-hour ABPM was performed using the SpaceLabs 90207 automated oscillometric device, programmed to register BP at 20-minute intervals for the day and at 30-minute intervals for the night. Valid registries had to fulfil a series of pre-established criteria, including ≥70% of SBP and DBP successful readings, 24-hour duration, and at least one BP measurement per hour.

Study Variables

Variables collected for each patient based on the interviews and physical examination at the time of visit and on data drawn from clinical records were defined and measured in accordance with contemporary European guidelines[16-18]. These included age, sex, weight, height, with body mass index (BMI) calculation, cardiovascular risk factors, such as smoking, diabetes mellitus, and dyslipidemia, and

history of cardiovascular disease (coronary heart disease, congestive heart failure, symptomatic peripheral artery disease, or cerebrovascular disease).

Mortality data

The date and cause of death were ascertained by a computerized search of the vital registry of the Spanish National Institute of Statistics (contract 20535 between the University of Barcelona and the National Institute of Statistics), which has been shown to be accurate and reliable with complete coverage[19]. Cause of death was determined by a nosologist from the death certificate and was coded according to the *International Statistical Classification of Diseases*, *Tenth Revision* (I00-I99 code for those of cardiovascular origin). For each study participant, follow-up was from the date of their recruitment visit in the blood pressure registry to the date of death or December 31st, 2019, whichever occurred first.

Statistical Analysis

Complete data were available for age, sex, all blood pressure measures, and BMI. Missing data for current smoking, diabetes, and dyslipidemia status was less than 1%, so patients with missing data were assumed not to have the condition. Data are presented as percentages for categorical variables and as mean ± SD for continuous variables. Differences in study variables between groups were assessed with the Pearson χ^2 for categorical variables and Student's *t* test for continuous data.

Differences in total and cardiovascular mortality between groups were summarized with hazard ratios (HR) and their 95% CI with one group in each comparison considered as the reference group. HR were estimated by Cox models, unadjusted and after adjustment for clinical confounders (age, sex, BMI, smoking, diabetes, dyslipidemia, and previous cardiovascular disease). Assessment of the proportional hazards assumption found some evidence against proportionality for some

of the resistant hypertension phenotypes. However, even in the presence of non-proportionality, the Cox HR still provides a useful summary statistic to describe the average association of the blood pressure index to risk over the follow-up period.

The SPSS for Windows version 25.0 software (IBM, Armonk, New York) was used for statistical analysis.

RESULTS

Patient disposition and group definition

The mortality cohort from the Spanish Registry included 59 124 patients, of whom 35 129 (59.4%) received antihypertensive drugs. Treated and controlled hypertension (8146 patients; 23.2% of treated patients) was defined as office BP below 140/90 mmHg while on treatment with 3 or less antihypertensive drugs (Figure S1). Treated but uncontrolled resistant hypertension (8577 patients; 24.4% of treated patients) was defined as office BP ≥ 140 and/or ≥ 90 mmHg, while treated with 3 or more antihypertensive drugs. Patients treated with 1 or 2 drugs with office BP ≥ 140 and/or ≥ 90 mmHg (uncontrolled non-resistant hypertension) were 17 554 (50%) while patients treated with 4 or more drugs with office BP < 140/90 mmHg (controlled resistant hypertension) were 831 (2.4%).

Differences between controlled hypertension and uncontrolled resistant hypertension according to office BP criteria

Compared to controlled patients, those with uncontrolled RH were older, and had more frequent obesity, diabetes, dyslipidemia, and cardiovascular disease at entry (Table 1). They also were more frequently treated with all medication classes (Table S1).

In Cox-regression models, both unadjusted and after adjustment for clinical confounders, uncontrolled RH was associated with an increase in mortality risk compared to controlled hypertension. After adjustment for clinical confounders, HR were 1.21 (95% CI: 1.12-1.30) for all-cause mortality and 1.33 (1.17-1.51) for cardiovascular mortality (Table 2). We performed two sensitivity analyses in uncontrolled RH patients who received a diuretic as a part of the antihypertensive therapy (N=7562; 88%) or who received treatment with a combination of renin-

angiotensin system blocker (either an angiotensin converting enzyme inhibitor, an angiotensin receptor blocker, or a direct renin inhibitor), a calcium channel blocker and a diuretic, as recommended by guidelines (N=4336; 50.6%). Hazard ratios for these groups in comparison to controlled hypertension were almost identical as those obtained in the whole group of RH (Table S2).

As mentioned, a small group of RH had clinic BP controlled (< 140/90 mm Hg) while on 4 or more antihypertensive medications. Compared with uncontrolled RH, they were slightly older and had an increase prevalence of previous cardiovascular disease (Table S3). They also had an increased risk of all-cause and cardiovascular mortality in comparison to controlled hypertension (Table S4), while no differences were observed in the risk of mortality between controlled and uncontrolled RH (Table S5).

Differences between ABPM-confirmed and white coat resistant hypertension

In the group of 8577 patients with uncontrolled RH, 24-hour ambulatory BP monitoring revealed elevated 24-hour BP (≥ 130 and/or 80 mmHg) in 5288 (61.7%), thus classified as having ABPM-confirmed RH. Otherwise, 24-hour BP was below 130/80 mmHg in 3289 (38.3%), thus classified as having white-coat RH, also known as pseudo-resistant hypertension according to ABPM. Patients with white-coat RH were slightly older, and were more frequently women and obese, and had less frequently diabetes, current smoking or previous cardiovascular disease, with respect to ABPM-confirmed RH (Table 3). With respect to medication, there were no relevant differences in the use of antihypertensive drugs classes (Table S6).

ABPM-confirmed RH was associated with an increased risk of all-cause and cardiovascular mortality compared to white-coat RH. In the confounder-adjusted model, HR for ABPM-confirmed RH versus white coat RH were 1.45 (95% CI: 1.32-1.60) and

1.68 (95%CI: 1.43-1.98), respectively for all-cause and cardiovascular mortality (Table 4).

Finally, ABPM-confirmed and white-coat RH were separately compared with the group of office-controlled hypertension. Although in the unadjusted model, both groups showed an increased risk of mortality, after the adjustment for confounders only ABPM-confirmed RH was associated with an increased mortality risk (HR: 1.36; 95% CI: 1.26-1.48 for all-cause mortality and HR: 1.56; 95%CI: 1.36-1.79 for cardiovascular mortality). In contrast adjusted HR for white-coat RH were not statistically significant (HR: 0.95; 95%CI: 0.86-1.05 and HR: 0.95; 95%CI: 0.80-1.14 for all-cause and cardiovascular mortality, respectively) versus controlled hypertension (Table 5).

DISCUSSION

The present study demonstrates that RH is associated with an increased risk of all-cause and cardiovascular mortality in comparison to controlled hypertension. Moreover, ABPM-confirmed RH has increased mortality rates compared to those with white-coat RH. Interestingly, this latter group does not show an increased risk of mortality compared to controlled hypertension. These results come from a very large cohort of RH patients defined by ABPM, and with a long follow-up (10 years).

The prognosis of RH compared to controlled patients has been investigated in several studies[8-10,20,21]. Daugherty et al[8], in a group of 3960 RH, followed for 4 years, found an increased risk of a combined endpoint of mortality, cardiovascular events, and chronic kidney disease development. However, in a sensitivity analysis, most of the increased risk was driven by chronic kidney disease development. In another study with 1870 RH patients included in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial, Muntner et al[10], found an increased risk of coronary, cerebrovascular, and renal events, as well as total mortality in comparison to non-RH. Another study with 2043 patients participating in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study found an increased rates of cardiovascular events and mortality in RH compared to those without RH[20]. Also data from the US National Health and Nutrition Examination Survey (NHANES) have shown that RH was associated with a 47% increased risk of cardiovascular mortality[21]. The largest data set reported was from Kaiser Permanente of Southern California[9], with more than 60,000 patients with RH. The retrospective study also found a poorer prognosis in RH with respect to controlled hypertension, although the increase in mortality was only 6%. However, in this study, there was no inclusion of ABPM to accurately define ABPM-confirmed RH versus white coat or pseudo RH.

Several years ago, we reported clinical differences between RH patients and those controlled on 3 or less medications[15]. The RH group was older, more obese, and with increased prevalence of cardiovascular risk factors and diseases. In the present analysis using the same patient registry, examining mortality for a period of almost 10 years, RH exhibited rates of mortality that almost doubled those in controlled patients. Although comorbidities were important in determining the prognosis, the survival model adjusted for such clinical confounders still revealed a significant increased risk of all-cause (21%) and cardiovascular (33%) mortality. These results confirm previous observations in the aforementioned studies[8-10,20,21]. However, the present study includes either a greater number of subjects examined and/or a longer follow-up, better characterization of BP using ABPM, and clinical management representative of usual practice in primary care.

The current guideline definition of RH emphasizes not only the number of drugs (at least 3) but also the preferred combination of drug classes, ideally, the triple combination of a renin angiotensin system blocker (either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker), a calcium channel blocker and a diuretic [2,6,7]. In our cohort, 88% of RH patients received a diuretic, and 50.6% received such a triple combination. Sensitivity analyses comparing these groups of patients with controlled hypertension yielded similar results as those obtained in the whole group of RH, suggesting that the presence of a diuretic or the type of drug combination used were not an important determinant of the prognosis. Moreover, in the small group of controlled RH (normal office BP while treated with 4 or more drugs), the risk of mortality was also increased with respect to controlled non RH, and similar to uncontrolled RH, suggesting that even controlling office BP by adding a fourth or a fifth drug is not enough to reduce the risk of RH. However, these particular results should be

viewed with caution, as the number of patients was relatively small and they had increased rates of previous cardiovascular disease, which suggests that this increased baseline risk was associated with an increased therapeutical effort in order to control BP.

We have previously reported from the same data registry, that when patients with ABPM-confirmed RH, i.e. with elevated 24-hour BP, are compared to those with white coat RH, i.e. those with normal BP on ABPM, the latter are characterized by less cardiovascular risk factors and comorbidities[4]. In the present analysis we have demonstrated that this translates into significantly different rates of all-cause and cardiovascular mortality, with the group of ABPM-confirmed RH showing increased hazard ratios (45% and 68%, respectively) in models adjusted for clinical confounders. Interestingly, when both groups of ABPM-confirmed and white-coat RH were separately compared to controlled hypertension, only ABPM-confirmed RH was associated with an increased risk of mortality in the confounder-adjusted model (36% and 56% for all-cause and cardiovascular mortality). In contrast, in the same confounder-adjusted model hazard ratios for the group of white coat RH were not statistically significant. These results are consistent with our previous report, in the general hypertensive population, indicating that white-coat hypertension is not associated with an increased risk of mortality[11].

These results emphasize the importance of out-of-office BP measurement in the stratification of risk in people with suspected RH. The importance of ambulatory BP monitoring in the prognostic evaluation of hypertension is now clearly established for the whole hypertensive population[11,22]. In RH patients, some previous studies also indicated that rates of cardiovascular events were closely dependent on 24-hour BP[12,13,23]. A recent study form Japan also demonstrated that only true RH was

associated with increased rates of CV events in comparison to controlled or uncontrolled non RH, whereas hazard ratios for white-coat RH were nonsignificant[14]. However, the study only included 643 RH patients, and mortality was not assessed. Our results reinforce these prior observations, but with a more definitive analysis, with substantially higher numbers of patients and number of deaths, as well as a much longer follow-up.

The present study has some limitations. First, recruitment of patients began in 2004. Since then, definitions of RH have been modified, including the type and doses of antihypertensive medications and greater recognition of the importance of treatment adherence. We have no information in the Registry regarding adherence to antihypertensive treatment. However, indirect measurements of adherence, as it can be used in routine clinical practice, are poorly correlated with direct measurements, such as serum or urine detection of drugs. With respect to the specific medications, as previously commented, the analysis of the subset of RH patients receiving the currently recommended triple combination yielded similar results as those obtained in the whole sample of RH patients. Another important limitation is that hazard ratios were substantially reduced after adjustment for clinical confounders. As these confounders were crudely measured, we cannot discard the possibility that the remaining association could be influenced by some residual confounding. Other limitations are derived from the use of data collected from a Registry, with antihypertensive treatment use collected at entry, without considering possible changes which occurred during follow-up. Moreover, the study cohort is a predominantly white population, and thus the findings may not apply to other ethnicities.

Perspectives

The present study, using a very large population cohort, with long term follow up (~10 years), shows that RH patients are at increased risk for all-cause and cardiovascular mortality when compared to people with treated and controlled hypertension. In addition, those with ABPM-confirmed RH have higher mortality rates than those with white-coat RH, and with the latter demonstrating no excess mortality when compared to those with controlled hypertension. The study clearly suggests the clinical importance of identifying true RH with respect to future prognosis, as well as the importance of differentiating between true RH and white coat RH according to ambulatory BP monitoring.

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Supplemental material: Figure S1, Tables S1-S6

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NOVELTY AND RELEVANCE

What is new?

- Resistant hypertension, confirmed by 24-hour ambulatory blood pressure elevation, is associated with an increased risk of all-cause and cardiovascular mortality, compared with either controlled hypertension or with “white-coat” resistant hypertension.
- “White-coat resistant hypertension is not associated with an increased risk of all-cause or cardiovascular mortality in comparison to controlled hypertension

What is relevant?

The prognosis of resistant hypertension is clearly dependent on 24-hour ambulatory blood pressure, as only the group with elevated values show an increased risk of all-cause and cardiovascular mortality

Clinical/Pathophysiological Implications?

- Ambulatory blood pressure monitoring should be performed in patients with resistant hypertension, . Blood pressure values obtained through 24-hour ambulatory blood pressure monitoring are powerful determinants of the risk of mortality in patients with resistant hypertension.
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Table 1. Demographic and Clinical Characteristics of Controlled versus Resistant Hypertension according to office BP

Parameter	Controlled Hypertension N=8146	Resistant Hypertension N=8577	P value
Male sex, %	50.9	52.1	0.141
Age, y	60.6 ± 13.4	65.4 ± 11.7	<0.001
Obesity*, %	38.7	54.7	0.001
Current smoker, %	14.1	11.8	<0.001
Diabetes, %	18.0	36.0	<0.001
Dyslipidemia, %	47.3	55.9	<0.001
Cardiovascular disease, %	14.9	19.2	<0.001
Blood pressure, mmHg			
Clinic systolic	127.0 ± 9.6	160.3 ± 17.2	<0.001
Clinic diastolic	76.7 ± 8.4	87.4 ± 12.2	<0.001
24-h systolic	121.7 ± 11.6	133.6 ± 15.5	<0.001
24-h diastolic	72.6 ± 8.8	74.0 ± 11.1	<0.001
Daytime systolic	124.4 ± 11.9	136.0 ± 15.7	<0.001
Daytime diastolic	75.2 ± 9.4	76.4 ± 11.5	<0.001
Nighttime systolic	114.4 ± 13.9	127.0 ± 18.2	<0.001
Nighttime diastolic	65.4 ± 9.2	67.7 ± 11.4	<0.001

Data expressed as mean ± SD or %. *Obesity defined as a body mass index ≥ 30 kg/m^2

Table 2. Hazard ratios for resistant hypertension in comparison to controlled hypertension (according to office BP) in relation to all-cause and cardiovascular mortality

Group			Total mortality		Cardiovascular mortality	
	Number of deaths (%)	Number of cardiovascular deaths (%)	Unadjusted model	Adjusted model	Unadjusted model	Adjusted model
Controlled hypertension (N=8146)	1080 (13.3%)	358 (4.4%)	Reference	Reference	Reference	Reference
Resistant hypertension (N=8577)	1942 (22.6%)	727 (8.5%)	1.72 (1.60-1.85)	1.21 (1.12-1.30)	1.94 (1.71-2.20)	1.33 (1.17-1.51)

Adjusted for age, sex, body mass index, smoking, diabetes, dyslipidemia, and previous cardiovascular disease

Table 3. Demographic and Clinical Characteristics of ABPM-confirmed versus White-coat Resistant Hypertension (RH) according to ABPM

Parameter	ABPM-confirmed RH N=5288	White-coat RH N=3289	P value
Male sex, %	56.1	45.7	<0.001
Age, y	65.1 ± 12.0	65.9 ± 11.1	0.001
Obesity*, %	38.7	54.6	0.001
Current smoker, %	13.5	9.1	<0.001
Diabetes, %	38.2	32.6	<0.001
Dyslipidemia, %	55.5	56.4	0.461
Cardiovascular disease, %	19.9	18.3	0.072
Blood pressure, mmHg			
Clinic systolic	163.0 ± 18.1	156.0 ± 14.8	<0.001
Clinic diastolic	88.3 ± 12.7	86.0 ± 11.1	<0.001
24-h systolic	142.5 ± 12.0	119.3 ± 7.7	<0.001
24-h diastolic	78.2 ± 10.8	67.2 ± 7.4	<0.001
Daytime systolic	144.9 ± 12.4	121.8 ± 8.2	<0.001
Daytime diastolic	80.6 ± 11.4	69.7 ± 8.0	<0.001
Nighttime systolic	135.9 ± 16.0	112.7 ± 11.0	<0.001
Nighttime diastolic	71.9 ± 11.0	60.9 ± 8.1	<0.001

Data expressed as mean ± SD, or %. *Obesity defined as a body mass index ≥ 30 kg/m^2

Table 4. Hazard ratios for ABPM-confirmed resistant hypertension in comparison to white-coat resistant hypertension (according to ABPM) in relation to all-cause and cardiovascular mortality

Group			Total mortality		Cardiovascular mortality	
	Number of deaths (%)	Number of cardiovascular deaths (%)	Unadjusted model	Adjusted model	Unadjusted model	Adjusted model
White-coat resistant hypertension (N=3289; 38.3%)	594 (18.1%)	201 (6.1%)	Reference	Reference	Reference	Reference
ABPM-confirmed resistant hypertension (N=5288; 61.7%)	1348 (25.5%)	526 (9.9%)	1.47 (1.33-1.61)	1.45 (1.32-1.60)	1.69 (1.44-1.99)	1.68 (1.43-1.98)

Adjusted for age, sex, body mass index, smoking, diabetes, dyslipidemia, and previous cardiovascular disease

Table 5. Hazard ratios for ABPM-confirmed and white-coat resistant hypertension separately compared with controlled hypertension in relation to all-cause and cardiovascular mortality

Group	Total mortality			Cardiovascular mortality		
	Unadjusted model	Age-sex adjusted	Fully adjusted model	Unadjusted model	Age-sex adjusted	Fully adjusted model
Controlled hypertension (N=8146)	Reference	Reference	Reference	Reference	Reference	Reference
ABPM-confirmed resistant hypertension (N=5288)	1.96 (1.81-2.13)	1.50 (1.39-1.63)	1.36 (1.26-1.48)	2.31 (2.02-2.64)	1.76 (1.54-2.01)	1.56 (1.36-1.79)
White-coat resistant hypertension (N=3289)	1.34 (1.21-1.48)	1.00 (0.90-1.10)	0.95 (0.86-1.05)	1.37 (1.15-1.63)	1.00 (0.84-1.19)	0.95 (0.80-1.14)

Fully adjusted model: Adjusted for age, sex, body mass index, smoking, diabetes, dyslipidemia, and previous cardiovascular disease