Prevalence of Resistant Hypertension in Non-Elderly Adults: Prospective Study in a Clinical Setting

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Abstract

Background: **In face of variable definitions and sampling criteria, the real prevalence of resistant hypertension in a clinical setting is unknown.**

Objective: **We investigated the prevalence of true resistant hypertension in an outpatient hypertension clinic.**

Methods: **True resistant hypertension was diagnosed when white coat phenomenon, lack of compliance and secondary hypertension were excluded in patients with blood pressure ≥ 140/90 mmHg in two consecutive visits, despite to be using three blood pressure-lowering agents, including a diuretic.**

Results: **In the total, 606 patients, with 35 to 65 years of age, mostly women, with BP of 156.8 ± 23.8 mmHg by 91.9 ± 15.6 mmHg and a BMI of 29.7 ± 5.9 Kg/m² were sequentially evaluated. One hundred and six patients using three BP drugs had uncontrolled blood pressure (17.5% of the whole sample) in the first visit. Eighty-six patients (81% of the patients with uncontrolled BP in the first evaluation) returned for the confirmatory evaluation. Twenty-five had controlled BP, 21 had evidence of low adherence to treatment, 13 had white coat phenomenon and 9 had secondary hypertension, leaving only 18 patients (20.9% of those uncontrolled in the confirmatory visit and 3% of the whole sample) with true resistant hypertension. Considering patients with secondary hypertension as cases of resistant hypertension, the prevalence of resistant hypertension increased to 4.5%.**

Conclusion: **The frequency of patients with true resistant hypertension in non-elderly patients is low in a clinical setting, and is not substantially increased with the inclusion of patients with secondary hypertension. (Arq Bras Cardiol 2012;99(1):630-635)**

Keywords: **Hypertension; prevalence; white coat hypertension; medication adherence.**

Introduction

Hypertension is among diseases with a large number of efficacious non-drug and drug therapies. Nonetheless, the proportion of patients with controlled hypertension has varied from 5.4% to 58% worldwide[1-4]. A large part of these patients have uncontrolled hypertension because they are not aware of their disease or do not adhere to the medical recommendations, but an unknown proportion of them are being treated and do not have controlled blood pressure. Patients with uncontrolled blood pressure taking appropriate doses of three blood pressure lowering drugs, including a diuretic, have resistant hypertension[5]. The exact proportion of such subjects was not clearly established to date, but has been assumed to be relatively common by countless reviews about the subject published in recent years. Based on secondary analyses of clinical trials, it has been estimated that perhaps 20% to 30% of study participants have resistant hypertension[5]. Findings from clinical trials may be not representative of unselected hypertensive patients, and in many studies, patients were not submitted to detailed evaluation of adherence and to the search of white coat phenomenon. Outside clinical trials, the description of the prevalence of resistant hypertension has been fragmentary and mostly based on secondary data. Moreover, the source of patients included in the surveys (the denominator for prevalence calculations) are quite variable. A secondary analysis of electronic records of patients treated for hypertension in an outpatient setting identified a prevalence of 12.4%[6]. Adherence to treatment and investigation of secondary causes was not reported in this survey, and the real prevalence can be somewhat lower. Ambulatory blood pressure (ABP) monitoring has shown also that a proportion of patients with resistant hypertension has white coat phenomenon[7], a condition that is associated with better prognosis[8]. A recently reported analysis of a large Spanish database identified 8,295 (12.2%) out of 68,045 treated patients with office resistant hypertension[9]. About a third of these patients had normal ABP, leading to an estimate of true resistant hypertension of 5,182 patients, corresponding to 7.6% of the whole sample. Again, adherence to treatment and secondary hypertension causes were not reported, suggesting that the real resistant patients are still fewer. Guidelines recognize that lack of adherence and secondary hypertension may influence the proportion of patients that have resistant hypertension[5], but it is unclear if

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patients with those conditions should be considered as having or not true resistant hypertension.

In this prospectively planned survey we investigated the prevalence of true resistant hypertension in an outpatient hypertension clinic, with confirmation by ABP monitoring and evaluation of adherence to treatment and of secondary hypertension.

Methods

This is an analytical cross-sectional study of patients attending to the outpatient hypertension program of our institution, whereas several observational studies and clinical trials have been carried out in the last 20 years. Detailed description of this cohort can be seen elsewhere[10-12]. The outpatient clinic is reference for patients with hypertension in our hospital and for the Public Health Network (Sistema Único de Saúde, SUS) in the metropolitan region of Porto Alegre, and is operating since 1988. More than 4.000 patients were evaluated since then. After the initial evaluation, most patients were followed-up in the Clinic, but around a third of them did not return after one year. Data from the extensive baseline evaluation and from the follow-up visits were collected in an electronic database specifically designed for the clinic. Currently, the clinic is mostly reference for patients with complicated hypertension. For this investigation, all consecutive patients aged 30-65 years that had medical appointments in the clinic in 2008, regardless of whether at the first evaluation or in follow-up visits, were submitted to an additional protocol. There were no criteria for exclusion. Patients with BP ≥ 140/ 90 mmHg, using three drugs in right doses, including a diuretic, were selected as having potentially resistant hypertension[13]. Recommendations for life style change and for the right use of the blood pressure agents were reinforced, without any modification of doses and agents, and the patients were asked to return for a confirmatory consultation. Patients who persisted with uncontrolled blood pressure in the second consultation were submitted to Ambulatory Blood Pressure (ABP) monitoring (Spacelabs 90207, Spacelabs, Redmond, WA). For analysis, normal blood pressure by ABP monitoring was mean 24 hours blood pressure below 130/80 mmHg. The investigation of secondary hypertension had been already done in most patients registered at the clinic and was completed in those that were still not investigated. The routine procedures employed to search for secondary hypertension included high clinic suspicion, mostly resistance to treatment, abnormality in urinalysis, creatinine or potassium, followed by the determination of aldosterone/renin ratio and renal artery Doppler when indicated. Obstructive sleep apnea was investigated in some patients as a part of a protocol of a case-control study[14], but they were not classified as having secondary hypertension, since this syndrome is still recognized as a risk factor for resistant hypertension and not a definite cause. Adherence to drug treatment was evaluated by the Morisky-Green test[15].

The cohort study that was the basis for patient selection was approved by the Institution Review Board, which is accredited by the Office of Human Research Protections as an Institutional Review Board. Since no departure from the recommended procedures for the evaluation and management of patients with hypertension, no inform consent was required. Descriptive statistics presented the proportion of patients with blood pressure uncontrolled after each step of confirmatory steps. No statistical testing of hypothesis was required.

Results

In the total, 606 patients were screened. Of these, 106 (17.5%) had blood systolic blood pressure equal of over 140 mmHg or diastolic blood pressure equal of over 90 mmHg despite of having a prescription of three blood pressure agents, including a diuretic. From these patients, 20 were newer patients and the remaining were being followed in the clinic for two to 14 years (mean 5.2 ± 4.4 years). The characteristics of these patients and the drugs and mean doses that they were using are shown in table 1. As can be seen in the table, the patients studied were mostly women with an average BMI close to obesity. The drugs that were being used included diuretics, beta-blockers, ACE inhibitors and vasodilators.

Eighty-six patients attended the confirmatory consultation (81%). Twenty five had office blood pressure within normal limits, 21 had low adherence, 13 had the white coat phenomenon, and 9 had secondary hypertension, leading to only 18 patients of the patients screened (3% of those originally evaluated) with uncontrolled blood pressure (Figure 1). If the prevalence among patients who did not attend the confirmatory consultation was twice the prevalence among those who did attend, another 8 patients would have truly resistant hypertension. As a result, the prevalence of true resistant hypertension in the initial sample would be 4.3%. Considering the patients with secondary hypertension as having resistant hypertension (n = 9) the prevalence would increase to 4.5%. Figure 2 shows flow-chart of the patients investigated.

Discussion

Our prospectively planned cross-sectional study conducted in an outpatient hypertension clinic provided two estimates of resistant hypertension. In a broad sense, 17.5% of our non-elderly patients were using three blood pressure agents (including a diuretic) and had uncontrolled hypertension. After the confirmatory consultation, and the exclusion of those who were non-adherent to treatment, or had secondary hypertension or white coat phenomenon, the prevalence dropped to only 3% of the original sampling.

The prevalence of resistant hypertension reported by clinical trials and other cohorts has been close to our first estimate[5]. Our final estimate was not quite far from the 7.6% reported by de la Sierra et al[9], and the difference may be explained by the checking of adherence and secondary hypertension in our study. A recent report based on data from the National Health and Nutrition Examination Survey from 2003 through 2008 estimated a prevalence of 12.8 (± 0.9) %[16]. Again, the patients were not submitted to the investigation of adherence to treatment and of the occurrence of a white coat phenomenon. It has been recommended that patients with controlled blood pressure taking four drugs should be diagnosed as having resistant hypertension, independently of the doses of the blood pressure agents[5]. This option could artificially increase

Table 1 – Characteristics of the participants and blood pressure agents and doses in use (n=106)

	N (%) or mean ± SD
Age	57.3 ± 10.6
Women	77 (73)
White skin color	80 (75.5)
Systolic blood pressure (mmHg)	156.8 ± 23.8
Diastolic blood pressure (mmHg)	91.9 ± 15.6
Duration of hypertension (years)	18.3 ± 9.0
Heart rate (bpm)	72.1 ± 14.3
BMI (Kg/m2)	29.7 ± 5.9
Waist circumference (cm)	97.3 ± 13.5
Smokers	
Never Ex-smokers Current	65 (61.3) 23 (21.7) 18 (17.0)
Fasting glucose (mg/dl)	113.8 ± 33.6
Total cholesterol (mg/dl)	199.8 ± 46.4
HDL-C (mg/dl)	54.3 ± 16.4
Serum creatinine (mg/dl)	0.9 ± 0.3
Amlodipine (mg/day) (n= 73)	10
Captopril (mg/day) (n= 69)	103.6 ± 58.5
Espironolactone (mg/day) (n= 14)	200 ± 104.1
Propranolol (mg/day) (n= 72)	222.8 ± 114.3
Metroprolol (mg/day) (n= 19)	200 ± 51.4
Hydrochlorothiazide/Amiloride (mg/day) (n= 12)	41.6 ± 12.3 /4.1 ± 1.2
Hydrochlorothiazide (MG/day) (n= 83)	57.1 ± 20.4
Enalapril (mg/day) (n= 10)	40 ± 20.0
Hydralazine (mg/d) (n= 38)	125 ± 64.3
Furosemide (mg/day) (n= 9)	80 ± 3.5

the number of resistant patients, since at least a proportion of them could be using one or more of the four antihypertensive patients in lower doses.

The concept of resistant hypertension at office and by ABP monitoring has been already proposed, including the definition of true resistant hypertension when blood pressure is uncontrolled at office and by ABP monitoring[9,17]. We propose that the concept of true resistant hypertension should require the exclusion of lack of adherence to treatment and secondary hypertension. Further description of prevalence of resistant hypertension in different settings could employ this definition, which seems to better describe the really difficult to treat patients seen in clinical practice. These patients should be further investigated to identify mechanisms of resistance and more efficacious therapies to control blood pressure. A condition that is not covered by the present criteria to define resistant hypertension is uncontrolled blood pressure at home (ABPM or home blood pressure measurement) and controlled at office (masked hypertension). This condition would be hard to identify, since the treatment should be oriented by blood pressure measured out of office.

Because of our sampling criteria, we were not able to describe the prevalence of true resistant hypertension in patients older than 65 years of age. Since the occurrence of systolic hypertension increases with age, a condition that has been more difficult to treat, the prevalence of true resistant hypertension in a broader age range is probably higher. On the other side, our clinic is a referral service for patients with hypertension, and a variable proportion of our patients has been referred because of difficult to treat hypertension. The prevalence of true resistant hypertension can therefore be still lower in non-elderly adults in other settings, such as in primary care services and in other clinical specialties.

Other limitations of our survey deserve mention. Patients who did not attend to the second evaluation could have more frequently true resistant hypertension and therefore the real prevalence could be somewhat higher. We performed a sensitivity analysis assuming that the prevalence among these patients would be twice the prevalence of those

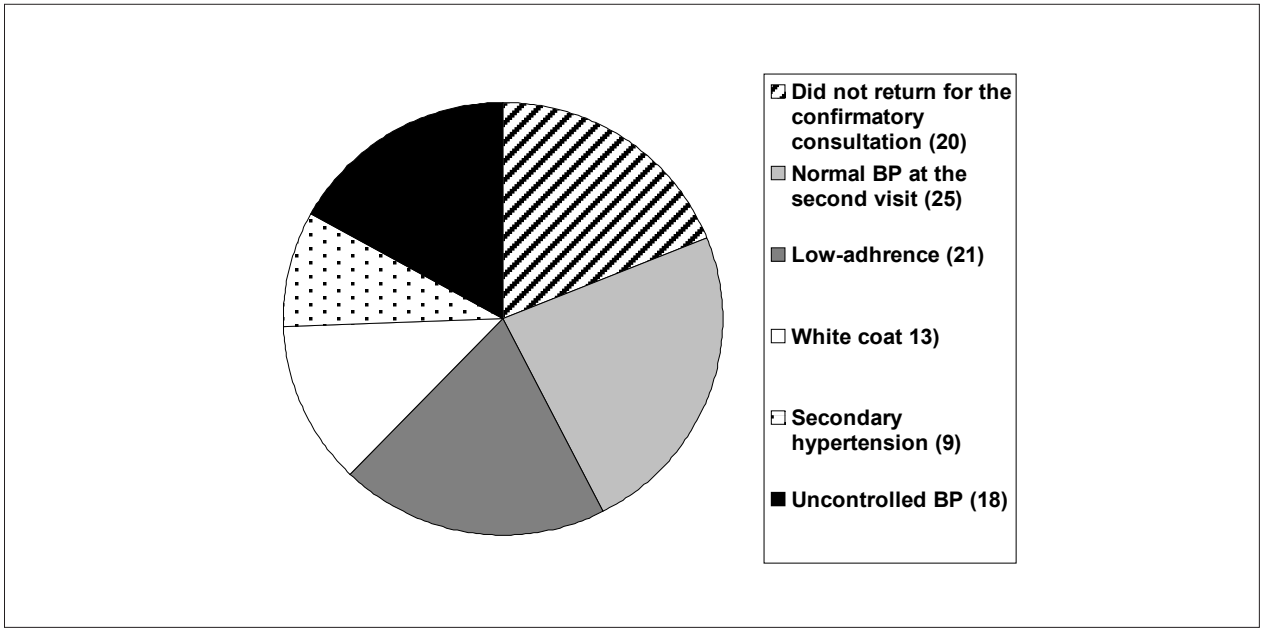

Figure 1 - *Outcomes in the confirmatory visit of patients with uncontrolled blood pressure at the screening consultation (106 out of 606 patients evaluated)*

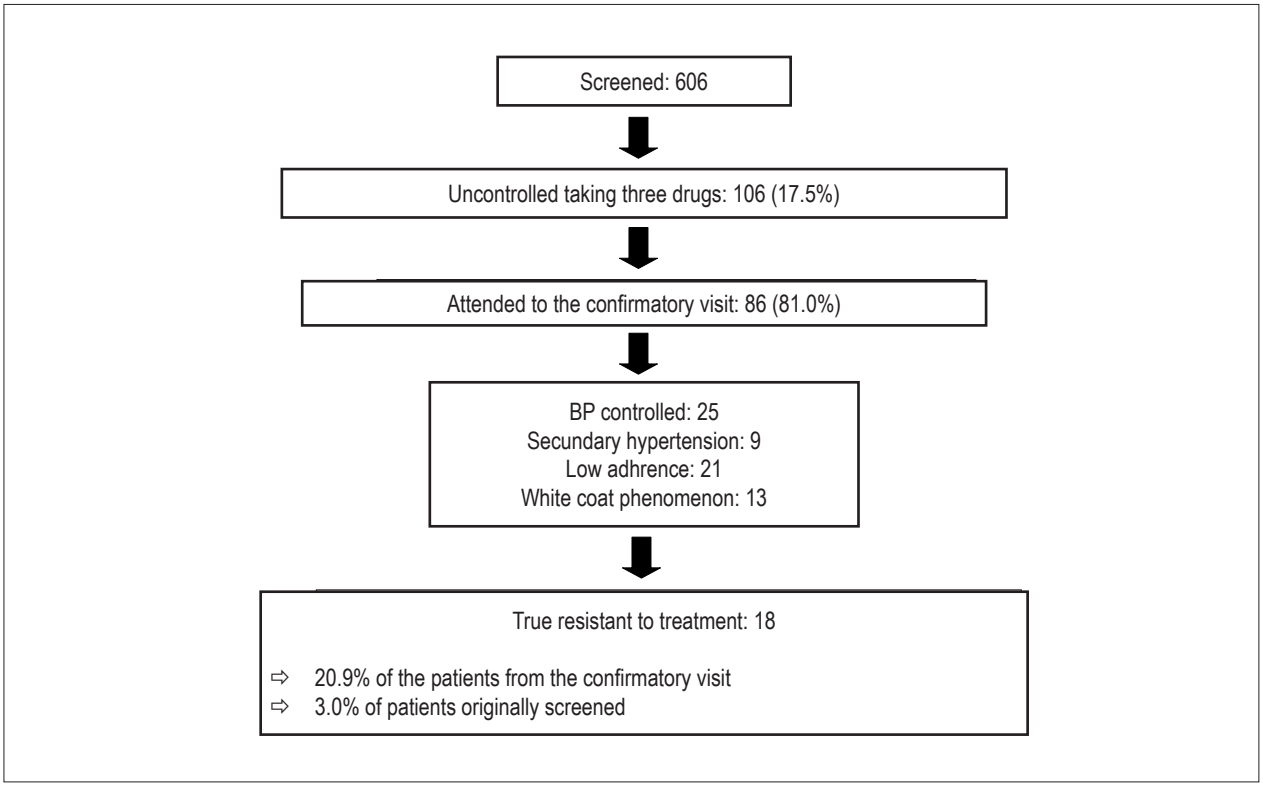

Figure 2 - *Flow-chart of patients evaluated for confirmation of true resistant hypertension*

who returned for the confirmatory visit, but even with this assumption, the prevalence would be below 5%. The restriction of investigation to only one center reduces the external validity of our findings, particularly because the higher proportion of women, which resulted from the uneven spontaneous demand of consultations by men and women. Among the strengths of our study are its prospective design, the confirmation of resistance by ambulatory blood pressure monitoring, the evaluation of adherence to treatment, and the systematic investigation of secondary causes of hypertension.

In conclusion, true resistant hypertension is infrequent in non-elderly patients with hypertension, and it is not substantially higher with the inclusion of patients with secondary hypertension. Homogeneous criteria to diagnose this condition are warranted.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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