Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **35** (4): 650-8 (2016)

Regular articles
Received: November 9, 2015
Revised version: January 24, 2016
Accepted: January 25, 2016

Hypertension, Associated Risk Factors and Mono-Drugs Prescription in a Primary Care Center

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***SUMMARY*. Hypertension is a risk factor to cardiovascular disease. Our objective was to analyze the prevalence of hypertension, risk factors and the prescription of mono-drugs in a Health Center of Mendoza, Argentina. An observational, descriptive, and retrospective study was performed. Age, sex, primary and secondary diagnosis, prescriptions and risk factors of outpatients who were assisted during April-June 2011 were recorded. International Classification of Diseases, the Anatomical Therapeutic Chemical Classification, and tables of blood pressure, cholesterol and triglycerides were used. Both sexes were equally affected by hypertension, prevalently between 50-69 years. The hypertension was associated with hyperlipidemia, anxiety, obesity, hypothyroidism, and diabetes. The drugs more prescribed were enalapril, atenolol, atorvastatin, aspirin, benzodiazepines and statins. Factors predisposing to the apparition of adverse reactions were comorbidities, polypharmacy and inappropriate prescriptions. Educational measures that contribute to a safe prescription of drugs in hypertension and strengthening the acquisition of healthy habits by patients are suggested.**

RESUMEN. La hipertensión es un factor de riesgo para la enfermedad cardiovascular. Nuestro objetivo fue analizar la prevalencia de hipertensión, factores de riesgo y la prescripción de mono-drogas en un Centro de Salud de Mendoza, Argentina. Se realizó un estudio observacional, descriptivo, retrospectivo. Se registraron edad, sexo, diagnóstico primario y secundario, recetas y factores de riesgo de los pacientes ambulatorios que fueron asistidos durante abril-junio de 2011. Se utilizaron las tablas de Clasificación Internacional de Enfermedades, la Clasificación Química Anatómo-terapéutica y los valores de la presión arterial, el colesterol y los triglicéridos. Ambos sexos fueron igualmente afectados por la hipertensión, predominantemente entre los 50-69 años. La hipertensión se asoció con la hiperlipidemia, la ansiedad, la obesidad, el hipotiroidismo y la diabetes. Los fármacos más prescritos fueron enalapril, atenolol, atorvastatina, aspirina, benzodiazepinas y estatinas. Los factores que predisponen a la aparición de reacciones adversas fueron las comorbilidades, la polifarmacia y prescripciones inadecuadas. Se sugieren medidas educativas que contribuyen a una prescripción segura de fármacos en la hipertensión y el fortalecimiento de la adquisición de hábitos saludables por los pacientes.

INTRODUCTION

Hypertension (HT) is one of the most important preventable causes of morbidity and mortality in the world. HT is a major risk factor (RF) for ischemic and hemorrhagic strokes, myocardial infarction, heart failure, chronic kidney disease (CKD), cognitive decline and premature death. HT without treatment is associated with a progressive rise in blood pressure (BP). The vascular and renal produced damages may also condition treatment resistance [1]. Although the current antihypertensive therapy has reduced the number of deaths, this disease remains a major medical and public health problem [2]. The increased prevalence of HT is consequence of the higher longevity of patients and of the higher prevalence of RF as obesity, sedentary and unhealthy diet. Its prevalence increases with age, especially affecting those over of 60 years [3].

BP is classified as optimal, normal, high normal; grade 1, 2, and 3, and HT isolated systolic [4]. From the etiopathogenic point of view, HT is

KEY WORDS: antihypertensive, hypertension, mono-drug, prescription, risk factors.

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ISSN 0326 2383 (printed ed.)
ISSN 2362-3853 (on line ed.)

classified as primary, of unknown cause, where cardiovascular RF affect it [3], and secondary, of known cause [5]; also, as stage 1 (BP ≥ 140/90), stage 2 (BP ≥ 160/100) and severe HT (BP ≥ 180 mmHg) [6,7].

The current HT treatment guides [1,4,6,8-11] have similarities and differences regarding to the classification of HT, BP target, and drugs considered of first choice.

Different drugs for starting the treatment are recommended: the angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) [11], ACEI, ARB, calcium channel blockers (CCB), or the thiazide-type diuretics [1]; thiazides to start in most patients, alternatively ACEI, ARB, CCB) [10]. Beta-blockers (BB) are drugs of fourth or third line except in one guide [4]. The levels for initiating drug treatment in low risk patients are ≥150/90 mm Hg [1,11,12].

The co-morbidities when prescribing antihypertensive drugs should be always considered [4].

The main goal of HT treatment is not only to lower the BP, but also reduce the risk of cardiovascular and renal complications [13]. Therefore, it is imperative the treatment of cardiovascular RF associated to HT [14].

All HT guides recommend changes in lifestyle, measures no-pharmacologic are essential because they reduce the use of drugs. The universal recommendations are: restriction of salt and alcohol, diet [15], reduced weight and waist circumference, physical exercise and smoking cessation [7].

All antihypertensive drugs compared to placebo are more effective in reducing morbidity [16,17]. These drugs have different impact on target organs and possible comorbidities, requiring individualized treatment choice [18].

Various antihypertensive drugs were compared for their ability to reduce morbidity and mortality due to cardiovascular RF [19-21]. Thiazides in low doses (ThLD) were upper to alpha-blockers, ACEI and CCB [19]. Also, the DM associated with these drugs does not increase the cardiovascular morbidity and mortality [22]. The choice treatment of HT in non-diabetic patients should be chlorthalidone or other thiazides possibly associated with amiloride or triamterene. Moreover, ThLD are recommend as drugs of choice in most patients, based on the results of clinical trials, availability and cost [10].

It is possible to choose an ACEI when it is not possible to administer a diuretic [23]. BB have been questioned as first-line treatment to prevent cardiovascular events, particularly stroke in elderly [24-26]. Nevertheless, BB are recommended to young hypertensive persons, and they are the treatment of choice in patients with ischemic heart disease, heart failure or atrial fibrillation [27,28]. The pharmacological treatment could start as monotherapy in HT grade 1 linked to cardiovascular risk (CVR) low to moderate [4,10]. In case of failure in BP control, the dose may be increased, or another drug at low doses may be added [29,30].

There is moderate evidence to support the initial treatment with an ACEI, ARB, CCB, or thiazide in the nonblack hypertensive population, including those with DM. A CCB or a thiazide are recommended as initial therapy in black hypertensive patients, including those with DM. In persons with CKD, moderate evidence was found that supports the antihypertensive therapy initial with an ACEI or ARB to improve kidney outcomes [1].

There are no agreements regarding the optimal treatment of second-line in uncomplicated HT, however it is proposed any drug, or use the BB or ACEI (ARB or CCB in case of intolerance or when inefficacy exist). BB and thiazides should be avoided in people with RF for DM, because they can trigger it [6]. ACE inhibitors reduce cardiovascular mortality and mortality from all causes, but the ARB does not [31]. In Argentina, HT is one of the main reasons for consultation in the adult population and its prevalence is estimated in 26-40% [32]. Only 50% of hypertensive patients knows your status, and the 13-20% are controlled and normotensive [33]. The prevalence of HT has increased in both sexes and with age. Moreover, the prevalence of HT in Mendoza was 37.2% [34].

The high prevalence of HT in Mendoza is known. The drug prescription is an individualized and dynamic clinical process, with prescribing patterns that can be strongly influenced by social, economic and/or promotional determinants [35]. In Argentina, and especially in Mendoza, few drug utilization studies have been conducted in primary care; furthermore, hypertensive patients are more vulnerable to suffer adverse reactions and to present associated RF and polypharmacy [2].

Considering the importance of HT, the vulnerability of patients with HT and prescriptive process variability in different areas and regions, we believe that is necessary the development of researches for gain knowledge about the HT,

associated RF, and the use and effects of drugs in hypertensive patients. Therefore, our objective was to analyze the prevalence of HT and its distribution by sex and age, the presence of RF and prescribing of mono-drugs in a Health Center (HC) of Godoy Cruz (Mendoza, Argentina).

MATERIALS AND METHODS

An observational, descriptive, and transversal study was performed in a HC of Godoy Cruz (Mendoza, Argentina). An authorization to carry this study out was obtained at Committee for Research and Teaching of the HC. The confidentiality of involved patients and physicians was reserved.

The data were obtained of different sources: System of Programed Medical Attention, epidemiological reports, external medical consultations and medical records of 61 chronic patients attended in Services of Cardiology and Internal Medicine from April to June 2011.

Records from the medical consultations of outpatients were obtained in each one of the services. The recipes that were extended to the patients were provided by the Pharmacy Service.

The following data were recorded: age, gender, primary and secondary diagnoses, number and type of prescribed drugs, BP values, total and LDL-cholesterol, triglycerides and other RF as smoking and sedentary.

Moreover, tables of values of BP, total and LDL-cholesterol, and triglycerides, were used [29,36]. The drugs and diagnoses were classified according to the Anatomical Therapeutic Chemical Classification System [37] and International Classification of Diseases [38], respectively.

The quality analysis of the prescriptions was performed according to current international guidelines for treatment of HT [1,4,6,8-11], the intrinsic potential therapeutic value of drugs (IPTV) [39,40], and their inclusion in the National Therapeutic Formulary [41].

The data were analyzed using the Software SPSS 18. The χ^2 statistical test (Chi square) was used to establish the possible association between categorical variables analyzed. A $p < 0.05$ was considered significant. Sex and age were expressed as a proportion of the total, to differentiate that observed in determined subgroups of that observed in the total population.

RESULTS

During April-June of 2011, 593 consults were registered (men 33%, women 67%). 61 chronic patients made a consult in the Service of Cardiology or Internal Medicine (men 28% and women 72%). Significant differences were not found when were compared the proportions of each sex in the analyzed group respect to the proportions of the total population (Fig. 1).

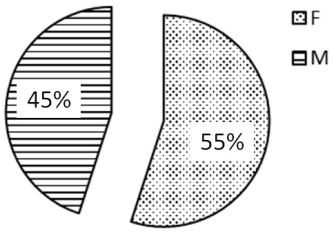

Figure 1. Distribution of patient attended in Medic Clinic and Cardiology (C) according to sex. The relation between the number of patients of C and the total of patients in each sex are represented. (C/total). F: female, M: male. There are not significant differences in C/total by sex (χ^2: NS).

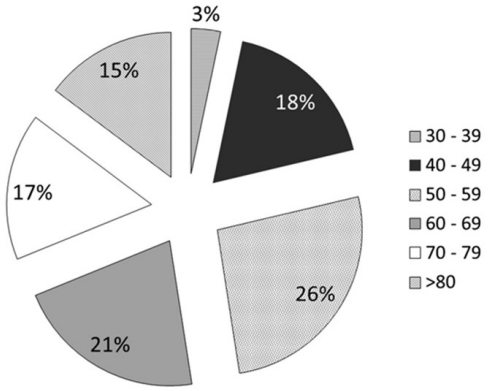

Figure 2. Distribution of patients according to age. The groups did not show significant differences (χ^2: NS).

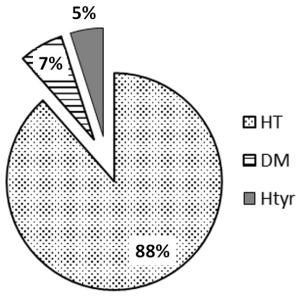

Figure 3. Principal diagnoses. Primary diagnoses are expressed in percentage. There are significant differences (χ^2: $p < 0.0001$; $n = 61$). HT: hypertension, DM: diabetes mellitus, Htyr: hypothyroidism.

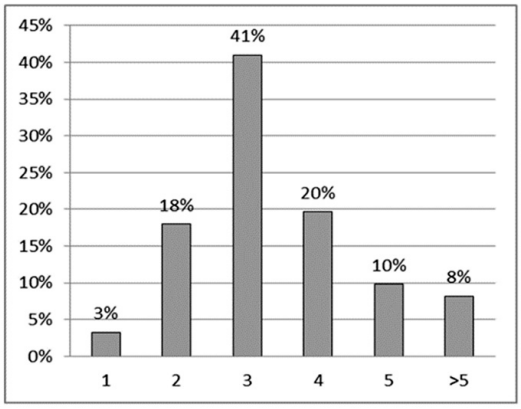

Figure 4. Number of pathologies by hypertensive patient expressed as percentage. There are significant differences (χ^2: $p < 0.012$).

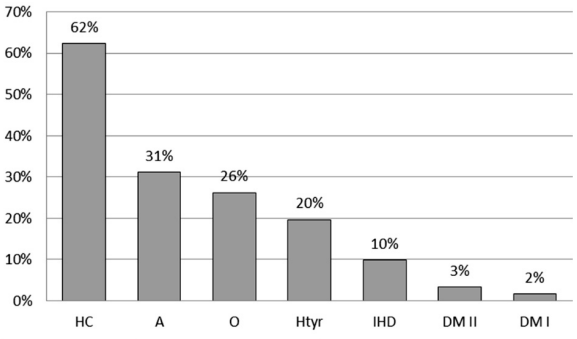

Figure 5. Concomitant pathologies. The most frequent comorbidities present in hypertensive patients are expressed in percentage. HC: hypercholesterolemia, A: anxiety, O: obesity, Htyr: hypothyroidism, IHD: ischemic heart disease DM II: diabetes mellitus type II, DM I: diabetes mellitus type I. There are significant differences (χ^2: $p < 0.0001$).

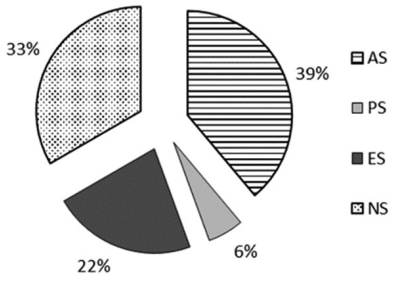

Figure 6. Snuff consumption. The snuff consumption in hypertensive patients is represented as percentage. There are significant difference (χ^2: $p<0.003$). AS: active smoker, PS: passive smoker, ES: ex-smoker, NS: nonsmoker.

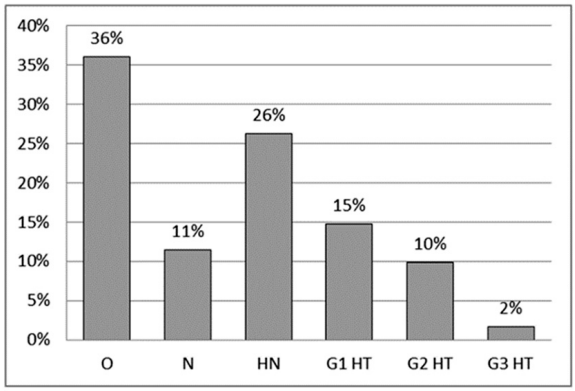

Figure 7. Blood pressure. Patients with blood pressure values within the ranges set forth in the classification of ESH/ESC [6], expressed as a percentage. There are significant difference (χ^2: $p < 0.02$). O: optimal, N: normal, HN: high normal, G1 HT, G2 HT, and G3 HT: Grade 1, 2 and 3 hypertension, respectively.

The distribution of hypertensive patients for age is show in the Fig. 2. The major number of hypertensive patients was found between 50-59 years old, but the differences were not significant.

Fig. 3 shows that the primary diagnosis was mainly HT, followed by DM and hypothyroidism.

In the majority of hypertensive patients, the number of pathologies or RF was two or more (Fig. 4).

The associated prevalent pathologies (or RF) were hypercholesterolemia followed by anxiety (Fig. 5).

The proportions of nonsmokers, smokers, former smokers or passive smokers are shown in the Fig. 6. A high proportion of smokers was observed among the hypertensive patients.

In Fig. 7, the reached BP values are displayed according to a hypertension treatment guide [4]. The hypertensive patients with optimal tension reached the highest percentage.

The blood lipid values are represented in Table 1. These have been classified according to a treatment guide [29].

If it is considered that there is polypharmacy when are prescribed four or more drugs simultaneously, 56% of hypertensive patients received polypharmacy (Fig. 8).

Fig. 9 shows the prescribed drugs; mainly correspond to enalapril, followed by atenolol, atorvastatin, aspirin and spironolactone. Meanwhile, benzodiazepines (clonazepam and alprazolam) reached 31%.

DISCUSSION

In a previous study, performed in San Luis

Cholesterol and Triglycerides							
Rank (mg/dL)		Female		Male		Total	
		n	%	n	%	n	%
Total Cholesterol							
Normal	<200	5	31%	3	33%	8	32%
High-Normal	200- 240	8	50%	4	44%	12	48%
High	> 240	3	19%	2	22%	5	20%
HDL Cholesterol							
Low	>40	2	13%		0%	2	8%
Normal F/M	>40/>35	5	31%	4	44%	9	36%
LDL Cholesterol							
Normal	<100		0%		0%	0	0%
High-Normal	100 – 160	3	19%	1	11%	4	16%
High	>160		0%		0%	0	0%
Triglycerides							
Normal	<150	5	31%	2	22%	7	28%
High-Normal	100 – 500	10	63%	7	78%	17	68%
High	>500		0%		0%	0	0%

Table 1. Values of cholesterol and triglycerides in hypertensive patients (according to ESH/ESC [29]).

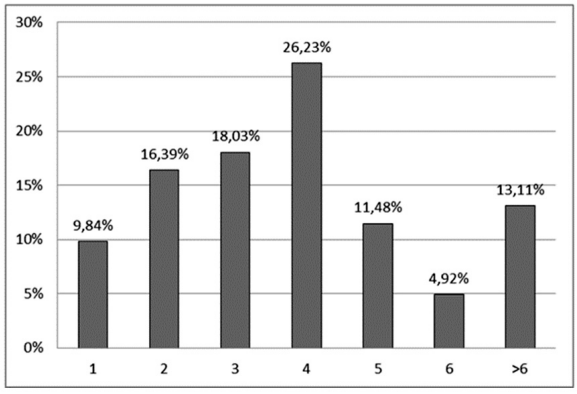

Figure 8. Number of drugs. Number of drugs prescribed simultaneously in hypertensive patients expressed in percentages. There are significant differences (χ^2: p< 0.0001), when are compared 1 to 3 drugs with 4 or more drugs (polypharmacy).

(Argentina) was detected a high prevalence of HT in the social security that was justified by the main attention of adults with chronic health problems [28]. In the current study, HT was the most prevalent diagnosis in the patients attended at Services of Internal Medicine and Cardiology, and its frequency was significantly higher than the anterior study [28], this difference would be justified by the analyzed target population.

An increase in the proportion of hypertensive patients with age was observed starting at 40 years, reaching the maximum between 50-59 years, being stable from the 60 years. Similar results were found in other studies [28]. It is known that the BP tends to increase throughout life, but in our case the increase began after 40 years.

The HT prevalence was similar in both sexes, such as recorded by Vara-González *et al.* [42], but this were different to that described by other authors that mainly found hypertensive men [43-46], or hypertensive women [47,48]. In men, the BP increases for unknown reasons, while in women increases after menopause that could be related to female hormones [43]. However, recently it was determined that the cardiovascular effects appear to be due to an older age in menopausal woman [49].

In this study, the number of comorbidities or risk factors presenting hypertensive patients is elevated, being prevalent of three to four concurrent pathologies. These results differ from those described by Mancia *et al.* [50], where was reported that the RF are mainly distributed between 1 to 2 RF in hypertensive patients. Patients that have multiple diseases or RF and that they use more medicaments for their treatment

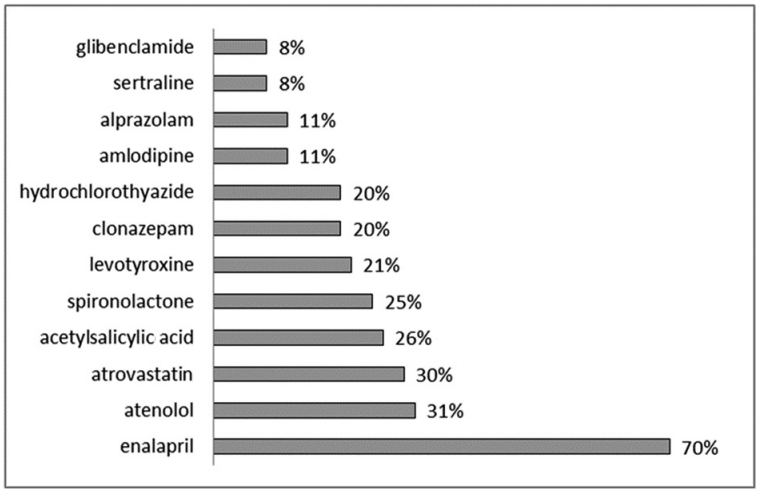

Figure 9. Drugs. Drugs more prescribed in hypertensive patients. The values are expressed as percentage. There are significant differences (χ^2: $p< 0.0001$).

are become more vulnerable to the occurrence of various side effects and drug interactions. The prevalent associated pathologies (or RF) were hypercholesterolemia, anxiety, obesity, hypothyroidism, smoking and high BP. The prevalence of smoking, which mainly comprises the active and passive smokers, is very high.

Although the majority of the patients analyzed achieved optimum or normal BP values (including high-normal), a percentage of 27% did not achieved the therapeutic objective. The lipids levels were: total cholesterol: high and high-normal, triglycerides: high-normal, and LDL-cholesterol: high-normal.

The antihypertensive pharmacological groups more prescribed corresponded primarily to ACEI, followed by BB, potassium-sparing diuretics, thiazides, and finally by CCB. These medicines were prescribed as mono-drugs, coinciding with the results of other study carried out in two hospitals, but not in the social security where was detected a high prescription of fixed-dose combinations [28]. The drug more prescribed was enalapril, coinciding with the findings in PROAPS-REMEDIAR [48].

Something that stands out is the high prescription of benzodiazepines, which reached 31%. Its indication in the treatment of HT largely of cases is inappropriate, probably because in many situations the origin of HT is associated mistakenly with anxiety. Also, it is necessary to make clear that the anxiolytics do not affect the course of HT because are not specific drugs for its treatment. In addition, for the treatment of HT is frequently prescribed for all life, however, appropriate treatment with benzodiazepines should not be extended beyond 4 weeks [51]. The use of these drugs for long periods is an important pharmacotherapeutic irrationality involving potential risks to the health of the population. This behavior may result from entrenched prescriptive habits and/or the pressure that patients often carried out on doctors to get these drugs.

Atorvastatin and acetylsalicylic acid were highly prescribed, but currently their use is very questionable. The consumption of atorvastatin and benzodiazepines is justified not only because they are the treatments of more frequent comorbidities (or RF), but because there are commercial interests and lack of transparency in scientific research [52].

The beneficial effect of statins on CVR depends on each patient. In change, the incidence of myopathy, hepatotoxicity and other undesired effects are independent of the CVR. Therefore, the relation risk-benefit of statins in CVR depends on each patient and is more favorable in patients at high CVR. The statin prescription to a person with low risk, unnecessarily increases the likelihood of adverse effects without providing any preventive effect [53].

Statins do not reduce the mortality in patients with low cardiovascular risk [54], and has not been yet demonstrated they have capacity to reduce total morbimortatality. However, the risk of adverse effects, such as muscle symptoms, DM, liver dysfunction, acute renal failure, cataracts, is the same, in consequence, the benefice/risk relation will be unfavorable.

The net benefit of aspirin in prevention of cardiovascular diseases remains unclear. Despite important reductions in nonfatal myocardial infarction, aspirin prophylaxis in people without prior cardiovascular diseases does not lead to reductions in cardiovascular death. Because the benefits are further offset by clinically important

bleeding events, routine use of aspirin for primary prevention is not warranted and treatment decisions need to be considered on a case-by-case basis [55].

ThLD were prescribed sparingly, confirming that they are underused despite knowing its clear benefits, that they are safe, well tolerated, comfortable and inexpensive [26]. Chlorthalidone is more effective than hydrochlorothiazide, as effective as an ACEI or CCB to prevent cardiovascular events, and more effective than an ACEI in reducing BP in black patients [56,57].

Evidences suggest that ThLD are first-line agents in HT, because they reduce morbidity and mortality [58]; in change, these drugs in high doses and BB are lower to ThLD [22]. BB are considered as third line agents, but still BB are recommended in ischemic heart disease, heart failure, atrial fibrillation or HT in young people [27]. ACEI and CCB seem to be equally effective, but there are less hard evidence to support them.

The monotherapy with thiazides, CCB or ARB as initial therapy of HT is recommended [9]. Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (alpha-blockers, ACEI, centrally acting agents or CCBs) may be added or substituted.

The European guidelines recommend monotherapy and combined therapy as initial therapies, while the American and Canadian guidelines recommend starting treatment with monotherapy and add the second drug when the desired goal is not achieved [59]. An estimated 40-60% of hypertensive patients achieved BP control with monotherapy and 60% of them will require the use of maximum dose [60,61]. In hypertensive patients with profile of "resistance", as obese, consumers of high amount of sodium and/or alcohol are used two or more drugs to act in several physiological mechanisms, reduce their dose and achieve greater and better control of HT [62].

In our study was detected a significant polypharmacy, which agrees with the authors that consider that more than two thirds of hypertensive patients require two or more antihypertensive agents [4,60,63,64]; but differs of other ones who suggest the monotherapy as initial treatment [1,9]. It is very desirable initiate and maintain the treatment with a single drug if the therapeutic goal is achieved, since the aggressions of drugs over the organism are minor, and possible interactions and the emergence of larger amount of adverse events are avoided.

Both sexes were equally affected by HT, and the predominant age group was the one that had more cardiovascular risk. HT was mainly associated with hyperlipidemia, anxiety and obesity. BP and blood lipids levels were optimal and normal; however, a percentage of patients had not a good control of HT. An elevated prescription of benzodiazepines, statins and aspirin was detected. Worryingly, the high percentage of comorbidities and polypharmacy, the prescription of drugs with an inadequate benefit/risk relation, since they are factors that predispose to the apparition of adverse reactions. Therefore, the implementation of educational measures that contribute to a safe prescription of drugs to HT and to acquisition of healthy habits by patients is suggested. Additionally, in the selection of any treatment should be taken into account the results of clinical trials and the nature and condition of each patient.

Conflicts of Interest. None of the authors of this manuscript have any financial interest that has influenced the results or interpretations of this manuscript.

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