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Well Controlled Blood Pressure in Turkish Patients: How Many Drugs Are Required to Attain and Maintain the Blood Pressure Goal?

Mustafa Temizel[1], Ugur Dilek Calap[1], Murtaza Cit[1], Mansur Azermir[1], Yucel Arman[2]

[1]Medicana International Hospital, Department of Internal Medicine, School of Medicine, Biruni University, Istanbul, Turkey
[2]Department of Internal Medicine, Okmeydani Training and Research Hospital, Istanbul, Turkey
Email: mustafatemi@yahoo.com.tr

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Abstract

Background: This study aimed to determine the number of antihypertensive agents required to achieve optimal blood pressure (BP) in Turkish hypertensive patients. **Material and Methods:** Totally 400 hypertensive patients (114 males and 286 females) were enrolled. BP was measured by patients at home twice a day. The patients were called for controlling in every four weeks, and those who had BP < 140/90 were not followed-up. In patients with BP > 140/90 drug, doses were increased or another antihypertensive drug added and the patients were continued to be followed-up. **Results:** In the first follow-up (on the 4th week), 152 (38%) patients, including 35 (31%) men and 117 (41%) women, attained the goal BP. The mean duration of hypertension in single, double, triple, and quadruple treatment groups was 6.2 ± 5.0, 6.8 ± 5.9, 8.8 ± 5.4, and 10.4 ± 6.6 years, respectively. In the beginning, the median number of agents used for each patient was 2.17. When the follow-up was concluded, the median of agents used for each patient was 2.72. **Conclusion:** Thirty-eight percent of participants had controlled hypertension in the first follow-up. Women had better BP control. The median number of agents required for attaining and maintaining BP goal was 2.72. More drugs are needed when hypertension gets longer.

Keywords

Blood Pressure, Antihypertensive Agents, Hypertension

1. Introduction

Hypertension is a major cause of morbidity and mortality, affecting almost every

organ system in the body. It is estimated that nearly one billion people are affected by hypertension worldwide [1]. Hypertension is associated with an increased risk for cardiovascular, cerebrovascular, and renal events [2] [3]. The Framingham Heart Study reported that the risk of major cardiovascular events increases with increasing severity of hypertension in all age groups [4]. Besides, Lewington *et al.* demonstrated that death from ischemic heart disease and stroke increases progressively starting from a systolic BP of 115 mm Hg and a diastolic BP of 75 mm Hg [5].

Practice guidelines for the management of hypertension recommend a BP goal of <140/90 mm Hg [6] [7]. More rigorous goals are recommended for patients with diabetes [6] [7] [8] and proteinuric chronic kidney disease [2] [7] [9]. However, despite the availability of several classes of antihypertensive drugs and several drugs in each class from which to choose, achieving BP goal is difficult in many patients.

The number of antihypertensive agents required to achieve optimal BP is unpredictable. It is difficult to find prospective studies aiming to determine the absolute mean number of drugs. Although some studies have information about the number of drugs used, this information is only presented as secondary data.

In this study, we aimed to examine the number of antihypertensive agents required to achieve optimal BP in Turkish hypertensive patients.

2. Material and Methods

In a total of 400 consecutive patients, previously diagnosed with essential hypertension, who attended the Medicana International Hospital Internal Medicine outpatient clinic between January 2016 and March 2017 were included in the study. The exclusion criteria included a history of notable cerebrovascular or cardiovascular disease within 6 months before the screening visit; abnormal serum electrolyte levels at screening (sodium < 135 mEq/l, potassium < 3.5 or >5.5 mEq/l); evidence of hepatic diseases (determined by any of the following: aspartate aminotransferase or alanine aminotransferase values greater than twice the upper limit of normal, a history hepatic cirrhosis); chronic kidney disease (determined by any of the following: a history of dialysis or a history of nephrotic syndrome and having an estimated glomerular filtration rate < 50 ml/min per 1.73 m^2 in the 3 months before screening); pancreatic disease or injury; uncontrolled, treated type 2 diabetes (glycosylated hemoglobin > 8.5%) and patients over 80 years of age.

Medication usage was assessed during the screening visit. Drug classes included angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-blockers, calcium channel blockers (dihydropyridine and nondihydropyridine), diuretics (thiazide and potassium-sparing), alpha-adrenergic receptor antagonists (Doxazosin), and central-acting drugs (Rilmenidin).

The patients were questioned for age, duration of hypertension, educational status, smoking habit, and diabetes status. Standardized anthropometric mea-

surements (weight, height) were obtained on individuals in light clothing without shoes. Body Mass Index (BMI) was calculated as body weight divided by height squared (kg/m^2). Serum lipid levels (LDL-c, HDL-c, VLDL-c, and Triglyceride) were measured in all patients.

All patients measured systolic and diastolic BP at home using their digital or manual sphygmomanometers. Patients were trained in the BP measurement method and tested. BP measuring devices were checked for the accuracy. BP was measured by patients twice a day (in the morning, and the afternoon or evening). The patients were followed for 36 weeks.

The patients were called for controlling in every four weeks, and those who had BP < 140/90 were not followed-up for longer. In patients with BP > 140/90 drug doses were increased or another antihypertensive drug added and continued to be followed-up. We noted the number of agents used for each patient at the beginning of the study and when the follow-up was concluded.

We compared groups for the duration of hypertension in terms of the numbers of drugs used.

The data analyses were performed with SPSS version 20 software for Windows. Kolmogorov-Smirnov normality tests were applied to examine whether the data showed normal distribution or not. The comparison between men and women, with controlled hypertension at week four, was made via chi-square test. The comparison between groups for the duration of hypertension was made via independent sample's t-test. A value of $p < 0.05$ was considered to be statistically significant.

3. Results

A total of 400 patients, 114 males (28.5%) and 286 females (71.5%), were evaluated in the study (Table 1).

Among the patients, 103 (25.75%) were using monotherapy, 155 (38.75%) were taking two different classes of drugs, 115 (28.75%) were using three different classes of drugs, 25 (6.25%) were taking four different classes of drugs, and 2 (0.5%) were taking at least five different classes of drugs (Table 2).

The ratio of ACE inhibitors, ARBs, β-blockers, calcium channel blockers, diuretics, α-adrenergic receptor antagonists, and central-acting drugs were 60.75%, 28.0%, 21.75%, 33.5%, 59.0%, 4.75%, and 3.75%, respectively (Table 3).

In the beginning, the median number of agents used for each patient was 2.17. In the first follow-up (week four) 152 (38%) participants, including 35 (31%) men and 117 (41%) women, had controlled hypertension and their follow-up did not continue. The female patients had significantly better BP control ($p < 0.001$).

The numbers (proportion) of patients achieving the BP goal at weeks 8, 12, 16, 20, 24, 28, 32 and 36 were 193 (48.2%), 268 (67.0%), 297 (74.2%), 330 (82.5%), 342 (87.0%), 361 (90.2%) and 364 (91.0%), respectively (Figure 1).

Thirty six (9%) patients left the study before their follow-ups were completed.

Duration of hypertension in single, double, triple, and quadruple treatment groups were 6.2 ± 5.0, 6.8 ± 5.9, 8.8 ± 5.4, and 10.4 ± 6.6 years, respectively. Duration of hypertension was longer in multiple drug groups (Table 4).

When the follow-up was completed and optimal BP control was provided the median number of agents used for each patient was 2.72.

Table 1. Demographic and baseline characteristics.

Variables	Group (n = 400)
Gender (n, %)	
Male	117 (29.25)
Female	283 (70.75)
Total	400 (100)
Age (years, mean ± SD)	58.05 ± 10.2
Education level (n, %)	
Illiterate	157 (39.25)
Literate	42 (10.50)
Primary school	181 (45.25)
High school-University	20 (5.00)
Duration of HT (years, mean ± SD)	8.3 ± 5.6
Diabetes presence (n %)	95 (23.75)
Smoker status (n %)	
Smoker	50 (12.5)
Non-smoker	350 (87.5)
Cholesterol (mg/dl)	218
LDL-c (mg/dl)	158
HDL-c (mg/dl)	42
VLDL-c (mg/dl)	33
Triglyceride (mg/dl)	193
BMI	30.93 ± 3.56
BMI distribution (n, %)	
Normal weight	59 (15.75)
Overweight	153 (38.25)
Obese	169 (42.25)
Morbid obese	19 (4.75)

HT: Hypertension, BMI: Body mass index.

Table 2. No. of antihypertensive medications used among patients.

No of drug classes	Number	P% (SE)
1	103	25.75 (2.7)
2	155	38.75 (2.8)
3	115	28.75 (2.2)
4	25	6.25 (1.2)
5	2	0.65 (0.7)

Table 3. Type of antihypertensive medications used among patients.

Antihypertensive medication class	Number	Percentage (SE)
ACEI	243	60.75 (2.8)
ARB	112	28.00 (1.7)
β-blocker	87	21.75 (3.1)
Calcium channel blocker	134	33.50 (3.2)
Diuretic	236	59.00 (2.5)
α-adrenergic receptor antagonist	19	4.75 (1.0)
Central-acting drug	15	3.75 (0.8)

ACE: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers.

Table 4. Comparison between groups regarding the duration of hypertension.

	Mono vs. double therapy	Mono vs. triple therapy	Mono vs. quadruple therapy	Double vs. triple therapy	Double vs. quadruple therapy	Triple vs. quadruple therapy
P	0.428	**<0.001**	**0.001**	**0.006**	**0.006**	0.213

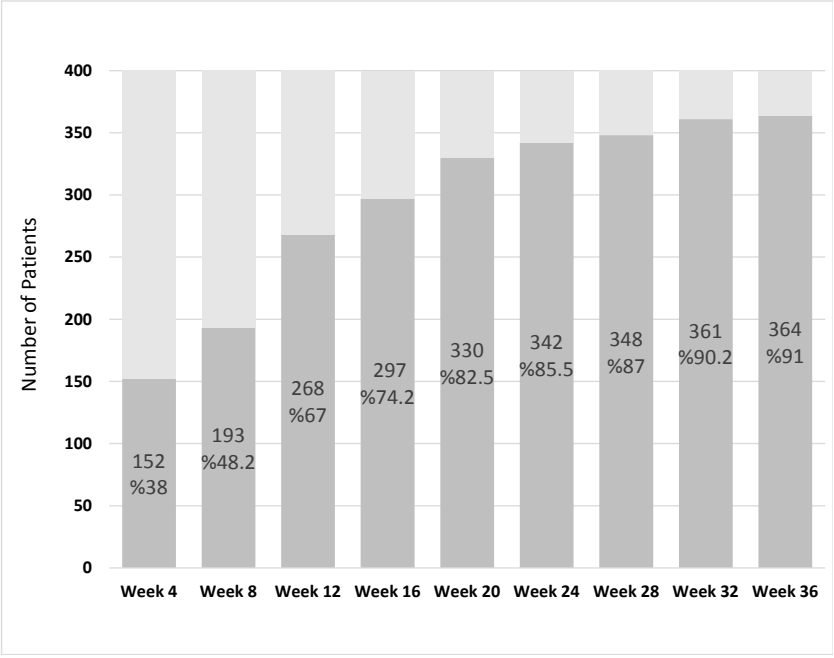

Figure 1. Number (%) of patients achieving BP goal.

4. Discussion

Although the risks associated with hypertension are known and the array of effective antihypertensive medications available, the control of BP remains suboptimal. Even in controlled randomized trials, where patient motivation and physician expertise are ensured, it has been difficult to achieve optimal BP [10].

In our study 152 (38%) participants reached the goal BP in the first follow-up. Hypertension control rates are in the average of those obtained in five European countries in men (31% in Turkey for values ranging from 14.3% in Spain to 39.7% in England) and is little higher in Turkish women (41%) than values ranging from 19.5% in Sweden to 40.5% in England [11]. In the US, 1999-2004 data from the National Health and Nutrition Examination Survey showed that the BP control rate in hypertensive subjects was 29.2% + 2.3% in 1999-2000 and 36.8% + 2.3% in 2003-2004 [12]. The control rates are not better in the rest of the world and vary considerably between countries and regions, and also vary within countries by age, gender, race/ethnicity, socioeconomic status, education, and quality of health care [13] [14]. Among higher risk populations with diabetes mellitus or chronic kidney disease (CKD), the proportion of uncontrolled patients is higher too. Of NHANES participants with CKD, only 37% and only 25% of participants with diabetes were having controlled BP < 130/85mm-Hg [15] [16].

Our findings showed also better BP control in women (41% vs. 31%). Data on the association of gender with hypertension control have been conflicting. In NHANES III (1988-1994), rates of awareness and control among hypertensive cases were significantly higher in women compared with men [15] [17]. However, in the 1999 to 2004 NHANES, there was no significant difference between men and women as a result of significant increases in treatment and control rates in men [18]. But many studies either in Europe [19] [20] or in the US [21] or other countries showed a better BP control in women [22]. Possible reasons for this could be a higher awareness and compliance, low alcohol intake, and higher health concern.

In the beginning of our study the median number of agents used for each patient was 2.17, but when the follow-up was completed and optimal BP control was provided the median number of agents used for each patient was 2.72. A study that analyzed the number of antihypertensive drugs used in different clinical trials reported that the median of agents used for each patient was 2.8 [23] [24] [25].

The majority of hypertensive patients need more than one antihypertensive agent to achieve BP targets. Numerous clinical trials conducted during the 1990s found that most hypertensive patients (including those considered to have a higher cardiovascular risk) required two or more medications to achieve BP goals [23] [26] [27]. In a recent randomized, double-blind study conducted on 2271 patients with stage 2 hypertension even in the triple therapy arm, BP control was achieved only by 71% of patients [28]. These results indicate that mul-

tiple-drug therapy is required in most patients with hypertension.

Current hypertension guidelines acknowledge that two or more antihypertensive agents are necessary for the majority of patients to reach BP goals associated with reduced risk of cardiovascular events [6] [7] [29]. The JNC-7 report suggests starting with two antihypertensive drugs in those patients with a systolic BP greater than 20 mmHg over the BP goal and/or greater than 10 mmHg over the diastolic goal [7]. European guidelines suggest combination therapy as a first step when initial BP is at least 160/100mmHg or when cardiovascular risk is high [6]. In this regard, the 2009 reappraisal of the European Guidelines on hypertension management recommends a more individually tailored approach for the management of hypertension, especially in high-risk patients [30].

Classically, guidelines recommended "start low, go slow". This meant that treatment should be initiated at low doses and with slow increases. But, several trials have shown that when the titration of drugs is very gradual, patients are at risk of presenting cardiovascular outcomes before BP goals are obtained, especially in those with diabetes or previous cardiovascular disease [31] [32].

Besides, guidelines recommend the selection of antihypertensive agents with different mechanisms of action to enhance the BP-lowering effect [6] [7]. The fact that hypertension is caused by interacting multifactorial mechanisms means treatment will be more effective if the drugs have different mechanisms of action [6]. Each constituent drug can neutralize counter-regulatory mechanisms activated by the other [33]. In addition, different pathways leading to elevated BP can be affected [6].

We also report a significant correlation between the duration of hypertension and the requirement for more drugs to achieve BP goals. Duration of hypertension in patients using multiple medications was longer. The need for higher dosage and more medication with the extension of the duration of hypertension is a common observation. Many questions arise about this subject. In fact, antihypertensive drugs are limited in terms of variation. Could the continuous effect of the same medication molecules on the same receptors cause a change in the receptor after a while? Could the non-response to the treatment be owing to the ineffectiveness caused by duration? Is a good BP control sufficient reason not to change the treatment? Would a change in medication from time to time be thought just to overcome resistance? Even though it is not a strong antihypertensive drug (but a different molecule) the benefit of adding spironolactone in reducing BP supports this thought. Recent trials have shown the benefit of adding spironolactone to the baseline strategy in RH patients [34] [35].

The present study has several limitations. Laboratory parameters were not routinely evaluated after the initiation of the study. Our study was not designed to test for effects on clinical outcomes. In the follow-ups of patients, we have preferred daily BP measuring at home, instead of periodically measuring BP in the office. Since all the patients had already been diagnosed with hypertension before and, most of them possessed a BP measuring device and a small percen-

tage of the patients acquired a measuring device via friends and relatives, which affected our decision accordingly. Moreover, either themselves or other persons at home, all the patients had experience in measuring BP. We checked the devices that were brought to us, but we cannot claim that all the devices were checked. Even though some setbacks occurred in daily measurements and making notes of BP, the patients made a satisfactory effort in this regard. The fact that the study was done in a metropolis like Istanbul, with understandable reasons, made it difficult for the patients to come for regular follow-ups. Therefore, the planned 24-week patient follow-up process was extended to 36 weeks.

5. Conclusion

More than 50% of hypertensive patients require two or even more drugs for the adequate control of their BP. To attain and maintain goal BP, using multiple drugs, changes in medications and more aggressive strategies should not be avoided. More drugs are needed when hypertension gets longer.

Ethical Statement

The study has been conducted and concluded with the Ethics Committee Approval (date 01.18.2016, decision no: 007) of our institution Biruni University, School of Medicine, Medicana International Hospital.

Informed consent was obtained from all participants; for illiterate participants, informed consent has been given from those authorized to represent them.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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