ACTA SCIENTIFIC MEDICAL SCIENCES

Volume 2 Issue 2 May 2018

Research Article

Therapeutic Schedules in Hypertension Control: All that Every Physician Should Know

Alfonso Lagi[1] and Simone Cencetti[2]

[1]*Internal Medicine, Villa Donatello Hospital, Florence, Italy*

[2]*Internal Medicine, Santa Maria Nuova Hospital, Florence, Italy*

***Corresponding Author:** Alfonso Lagi, Internal Medicine, Villa Donatello Hospital, Florence, Italy.

Received: March 14, 2018; **Published**: April 14, 2018

"If everyone is thinking alike, then no one is thinking".

Benjamin Franklin

Abstract

Background: Hypertension is a leading risk factor for death and disability and guidelines and statements advice many suggestions for its control. Unfortunately, they are not enough and to handle the hypertension in real world is challenging. Overall the proportion of hypertensive individuals whose condition is treated or controlled with medication remains low but very difficult to establish.

Method: Drug treated hypertensive patients (18 - 80 yo) were enrolled. The study was done using a first group of hypertensive patients with pharmacological treatment with three or four drugs. A second comparison group was formed of hypertensives that took one or two drugs. Patients were subjected to a four-month follow-up so that they have the initial and the remote data. Side effects were considered, in particular the appearance of asthenia, syncope and/or lypothimia and a reduction in renal function. The univariate analysis was made for age, sex and for the number of drugs used vs the value of Pa. Subsequently, a multivariate analysis was performed between the significant univariate variables.

Results: The number of patients enlisted in the study was 114 (58 males, mean age 61 years). The result is that the arterial pressure mean of patients taking 3 or more drugs (52 pts) are significantly different from the others (62 pts). The second result is that exist a trend of odd ratio among the different groups estimated at 2 (CI 95% 1,38 - 3,06) for each step. In other words the increase of one drug added to previous double the probability to go at target and so to have a control of arterial pressure.

Discussion and Conclusions: Many hypertensive patients have complex form of the disease, so that their hypertension is hard to treat, due to resistant hypertension or because complicated by a range of comorbidities. More drugs major effect. This may be the most important outcome of the work. The work shows how combined treatment is much more beneficial to bring the patient to a target.

Keywords: Hypertension; Systolic Blood Pressure Intervention Trial (SPRINT); Cardiovascular Disease

Introduction

Hypertension is a leading risk factor for death and disability, including stroke, accelerated coronary and systemic atherosclerosis, heart failure, chronic kidney disease and death from cardiovascular causes.

In the Systolic Blood Pressure Intervention Trial (SPRINT), adults at high risk for cardiovascular disease who received intensive systolic blood-pressure control (target, < 120 mm Hg) had significantly lower rates of death and cardiovascular disease events than did those who received standard control (target, < 140 mm Hg) [1]. The data was implemented in the recent GL ACC/AHA [2].

To handle the hypertension in real world is challenging. No more 50% of hypertensive people have a real control of their hypertension with great differences between one nation and another and between different places in the same country for age and ethnicity [3,4]. Overall the proportion of hypertensive individuals whose condition is treated or controlled with medication remains low but very difficult to establish.

This work is a cohort study has not sponsored and was to give contribution to define the efficacy of pharmacological control with dietetic and physical activity on the hypertension in a population study.

Because hypertension is the world's most common and modifiable cardiovascular risk factor [5], the aim was to discover if the number of antihypertensive drugs is linked with the better hypertension control (primary outcome) or whether the result is influenced by dietetic and physical activity.

Methods

A cohort study was conducted using a first group of hypertensive patients with pharmacological treatment with three or four drugs. A second comparison group was formed of hypertensives that took one or two drugs.

Drug treated hypertensive patients were enrolled. They come to medical check sent by their own physician who prescribed their antihypertensive therapy.

The experimenters' intervention was to define dietary and behavioural rules for the control of hypertension without affecting the choice of drugs.

The patients were subjected to history, physical examination and clinical test when it needs. Comorbidities like diabetes, proteinuria, renal failure and weight and previous cardiovascular diseases like coronary artery disease, cardiac diseases, stroke, peripheral, aortic, carotid, renal disease were considered. Patients were subjected to a four-month follow-up so that they have the initial and the remote data.

Drug surveillance was done to ensure patient compliance and it was evaluated with particular and specific question. The demonstration of a correct dietetic and physical activity control was researched by BMI change from baseline. Side effects were considered, in particular the appearance of asthenia, syncope and/or lypothimia and a reduction in renal function. The age has to be of at least 20 years and no more than 80 years

Study measurement

Arterial blood pressure value was based on a mean of three blood-pressure measurements at an office visit while the patient was seated and after 5 minutes of quiet rest; the measurements were made with the use of an automated measurement system (Model 907, Omron Healthcare) by a nurse while the patient seated in the waiting room.

Patients were scheduled according to the blood pressure value at the control after 4 months from the first visit. BMI was evaluated as + or - variation compared to 4 months earlier.

The study was approved by the institutional review board at each participating study site. The steering committee designed the study, gathered the data, made the decision to submit the manuscript for publication, and vouches for the fidelity of the study to the protocol.

Statistical analysis

Data were analysed by Stata system and a test t of Student for paired data. The univariate analysis was made for age, sex and for the number of drugs used vs the value of Pa.

Subsequently, a multivariate analysis was performed between the univariate variables that had a significance value for $p < 0.5$: sex, therapy (drugs = or < 2 o = o > 3), diabetes mellitus and BMI considered as a binary system (reduced or unchanged and increased). The level of significance of $p < 0.05$ was chosen.

An independent data and safety monitoring physician (Ph.L.) monitored the results and safety events. The primary analysis was done in the intention-to-treat population.

To analyse the results, the patients were scheduled before in two groups, three and more or less than three drugs and after in in four group (1-4) related to the number of drug utilized in the hypertension control. Target for arterial pressure was defined at value equal or less than 140/80 mmHg.

Result

The number of patients enlisted in the study was 114 (58 males, mean age 61 years). Only 12 patients were excluded for different reasons (there will not to cooperate, nor compliance or age not in range). Data are referred to the second control after 4 months of follow up.

The result is that the arterial pressure mean of patients taking 3 or more drugs (52 pts) are significantly different from the others (62 pts). The comparison of the arterial pressure mean value is 156/87 mmHg vs 168/85 mmHg with statistical significance ($p < 0.04$ for systolic and $p = 0.007$ for diastolic arterial pressure). In other words the patients who use three or four drugs have the arterial pressure mean less than those who use one or two drug. The division of patients in four group shown in table 1.

	Male (mean age yo)	Women (mean age yo)	Arterial pressure (mean mmHg)
Group 1	14 (52)	17 (58)	169/95
Group 2	16 (62)	15 (63)	167/96
Group 3	14 (60)	12 (64)	162/90
Group 4	14 (66)	12 (64)	151/85

Table 1: Sharing of patients in the groups.

The groups are comparable for age ($p < 0.98$), number of patients and sex differences.

The second result is that exist a trend of odd ratio among the different groups estimated at 2 (CI 95% 1,38 - 3,06) for each step. In other words the increase of one drug added to previous double the probability to go at target and so to have a control of arterial pressure.

In table 2 is shown the number of patient at target.

Groups and number of patients	Number of patients at target (Pa < 140/90 mmHg)	% of patients at target
Group 1 (31)	3/31	10
Group 2 (31)	2/31	6
Group 3 (26)	6/26	23
Group 4 (26)	12/26	46

Table 2: Patients at target in the different groups.

Eighteen patients on 52, i.e. the 34% of patients in the group 3 and 4, respectively 23 and 46% are in target vs 8% in the group 1 and 2, respectively 10 and 6%.

The difference between the initial BMI and that of 4 months later showed a decrease in each group with different statistical significance (Table 3).

Patients with a blood pressure target showed a significant association with the change in BMI less (OR 11.8 CI 1.4 - 94.8). Similarly, the association with more than 2 drugs showed a significant association (OR 4.8 CI 1.6 -13.9). No statistical significance was detected with diabetes mellitus, age and sex. The table 3 resumes the results.

	Diabetes: target/total	%	Previous CV disease*: target/total	%	Presence of cardiovascular disease**: target/total	%	Change BMI	p
Group 1 (31)	1/13	8	1/11	9	0/14		-0.5	0.03
Group 2 (31)	1/16	6	1/12	8	1/17	6	-0.3	NS
Group 3 (26)	1/12	8	0/9		0/16		-0.8	0.01
Group 4 (26)	5/12	42	6/11	54	8/14	57	-1.6	0.01

Table 3: Sharing of the patients related to previous or actual diseases.

*:Acute myocardial infarction, angina, Ao coronary bypass o coronary stent, stroke

**: Ventricular hypertrophy, Left branch bundle block; atrial fibrillation, albuminuria, renal failure, abdominal aortic aneurism, carotid atherosclerosis, Ankle brachial index < 0.9

The group number 4, with major number of target for the arterial pressure (46% see table 2), shows that are the subjects suffering from previous or present cardiovascular disease to at target more frequently (54 and 57% respectively).

	Astenia	Syncope/Lipothymia	AKD*
Group 1 (31)	3	1	
Group 2 (31)	0	1	1
Group 3 (26)	6	3	2
Group 4 (26)	6	5	3

Table 4: Relationship between collateral effects and therapy.

A: Asthenia

*: Acute Kidney Disease: increase SCr more than 50% during next three months.

Discussion

Many hypertensive patients have complex form of the disease, so that their hypertension is hard to treat, due to resistant hypertension or because complicated by a range of comorbidities.

Recommended strategies include restriction of dietary sodium intake below 1500 mg per day [6], weight loss if the patient is overweight or obese [7]. Each of these strategies is likely to reduce systolic pressure by 3 to 8 mm Hg and diastolic pressure by 1 to 4 mm Hg [8].

The arterial pressure mean of the subjects taking three or more drugs is significantly less than the others ($p < 0.04$ and $= 0.007$). This relief appears original and novel even if the guidelines emphasize that monotherapy is effective only a limited number of hypertensive patients and that most patients require the combination [9]. A meta-analysis of more than 40 studies has shown that combining two agents from any two classes of antihypertensive drugs increases the BP reduction much more than increasing the dose of one agent [10].

Further advantage of therapy of combination is that there are physiological and pharmacological synergies between the different classes of agents, that may not only justify a greater blood pressure reduction but also cause fewer side-effects and may provide larger benefits than those offered by a single agent [9].

Combination therapy is known to reduce the harmful effects of hypertension [11]. It is a few weeks after its beginning [12] that it shows its effectiveness in terms of reducing blood pressure. In our work there is an additional data that the pressure control progressively improves as the number of drugs increases.

With regard to the hypertensive population, the number of subjects taking three or more drugs is high in relation to the total number of subjects enrolled. They can be termed resistant hypertensives because resistant hypertension is defined as the achievement of the pressure target with pharmacological regimen with over three classes of drugs at appropriate doses, one of which is represented by a diuretic [13,14]. In the cases presented, half of the population can be defined as resistant hypertension, going well beyond the 10% incidence usually considered [15]. The data is the consequence of the criteria used in the choice of cases. In fact the purpose and method of work have selected resistant hypertensives because they were enrolled subjects with high number of drugs.

Non-adherence to therapy may be a cofactor responsible of the failure of response and this happens when 2 or 3 or more pills are used at different hours in the day. In our work the problem has been overwhelmed from the design of the study. So, we can offer cases in whom only the sure effect of the drugs and their combination is considered. In the real world, adherence to treatment is an important problem capable of nullifying the result of programmed therapy. The presence of complications and the need for secondary prophylaxis seems a sufficient reason to motivate the patient because over half of the cases in the group that takes 4 or more drugs are targeted (Table 3).

BMI measures excess weight and it predicts future morbidity and death. Therefore, it is an appropriate measure for screening for its health risks. It is used in studies of hypertension as a measure of risk [16-18]. Its change has been taken as index the dietary behaviour and the physical activity regimen of the subject. Also the control of BMI and its decrease appear to be related to the control of hypertension with a statistical weight higher than that of drug therapy [2]. In our data BMI results less effective in hypertension control. In group 1 and 2, in fact, despite having a significant decrease in BMI in the follow-up, do not have enough patients to target what instead happens in group 4 and to a lesser extent in group 3.

The presence of diabetes don't affect the result ($p = 0.94$) while the previous cardiovascular disease support the pressure control [19] (Table 3). In other words, secondary prophylaxis seems to motivate the patient more.

Finally, it is evident that the use of many drugs associates with the appearance of side effects (Table 4). None of them has been so serious as to discontinue therapy and it appears to be a known and predictable phenomenon when looking for an ambitious target [1].

Conclusion

More drugs major effect. This may be the most important outcome of the work. The work shows how combined treatment is much more beneficial to bring the patient to a target. The new GLs of the ACC/AHA move in this direction underlining that most adults with blood pressure sufficiently elevated to warrant drug therapy should be treated initially with 2 agents. If there are no compelling indications for choice of a particular drug class, the guideline suggests a diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or calcium channel blocker as acceptable first-step agents but identifies thiazide diuretics (especially chlorthalidone) and calcium channel blockers as good options for monotherapy. In addition to careful BP measurement, the new guideline highlights the increasingly important role of out-of-office BP readings. It also emphasizes contemporary strategies to improve BP control, including ways to successfully implement and sustain nonpharmacological interventions, improve medication

adherence, use a structured team-based approach to care and take advantage of health information technology [2].

Bibliography

1. The SPRINT Research Group. "A randomized trial of intensive versus standard blood-pressure control". *New England Journal of Medicine* 373.22 (2015): 2103-2116.

2. Whelton PK., *et al*. "2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines". *Journal of the American College of Cardiology* (2017).

3. Olives C., *et al*. "Prevalence, awareness, treatment, and control of hypertension in United States counties, 2001-2009". *PLoS One* 8.4 (2013): e60308.

4. Ikeda N., *et al*. "Control of hypertension with medication: a comparative analysis of national surveys in 20 countries". *Bulletin of the World Health Organization* 92.1 (2014): 10C-19C.

5. Forouzanfar MH., *et al*. "Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015". *Journal of the American Medical Association* 317.2 (2017): 165-182.

6. Aburto NJ., *et al*. "Effect of lower sodium intake on health: systematic review and meta-analyses". *British Medical Journal* 346 (2013): f1326.

7. Neter JE., *et al*. "Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials". *Hypertension* 42.5 (2003): 878-884.

8. Whelton PK., *et al*. "Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of non-pharmacologic interventions in the elderly (TONE)". *Journal of the American Medical Association* 279.11 (1998): 839-846.

9. Mancia G., *et al*. "2013/ESC Guidelines for the management of arterial hypertension". *Journal of Hypertension* 31.7 (2013): 1281-1357.

10. Wald DS., *et al*. "Combination therapy vs. monotherapy in reducing blood pressure: meta-analysis on 11 000 participants from 42 trials". *American Journal of Medicine* 122.3 (2009): 290-300.

11. Gradman AH., *et al*. "Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study". *Hypertension* 61.2 (2013): 309-318.

12. Flack JM., *et al*. "Efficacy and safety of initial combination therapy with amlodipine/valsartan compared with amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study". *Journal of Human Hypertension* 23.7 (2009): 479-489.

13. Calhoun DA., *et al*. "Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research". *Hypertension* 51.6 (2008): 1403-1419.

14. Williams B., *et al*. "Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV". *Journal of Human Hypertension* 18.3 (2004): 139-185.

15. Schmieder RE., *et al*. "ESH position paper: renal denervation - an interventional therapy of resistant hypertension". *Journal of Hypertension* 30.5 (2012): 837-841.

16. Jackson C., *et al*. "Joint effects of physical activity and BMI on risk of hypertension in women: a longitudinal study". *Journal of Obesity* (2014): 271532.

17. Channanath AM., *et al*. "Impact of hypertension on the association of BMI with risk and age at onset of type 2 diabetes mellitus: age- and gender-mediated modifications". *PLoS One* 179.4 (2014): e95308.

18. Mu M., *et al*. "Dietary patterns are associated with body mass index and bone mineral density in Chinese freshmen". *Journal of the American College of Nutrition* 33.2 (2014): 120-128.

19. Lagi A., *et al*. "Compliance with therapy in hypertensive patients". *Internal and Emergency Medicine* 1.3 (2006): 204-208.

Volume 2 Issue 2 May 2018