Combination antihypertensive therapy in controlled hypertensive patients in a private hospital of Lima

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ABSTRACT

Objective: To describe the use of combination antihypertensive therapy in a sample of controlled hypertensive patients confirmed by ambulatory blood pressure monitoring (ABPM). **Methods and Materials:** The information was collected from medical records of patients older than 18 years old, who visited the cardiology procedures office in a private hospital of Lima, diagnosed with controlled high blood pressure (HBP) documented by ABPM and who did not change antihypertensive therapy for at least one month before taking the ABPM. **Results:** A sample of 75 patients with an average age of 59.5 years old was selected, most of which were women (64%). Combination therapy was prescribed for 47% (n=35) of patients. In the group of combination therapy the average number of antihypertensive drugs was 2.4; predominant schemes were: angiotensin II receptor blocker (ARB-II) + hydrochlorothiazide (HCT) in 51% of cases and ARB-II + HCT + calcium channel blocker (CCB) in 17% of cases. **Conclusions:** Combination therapy was predominant among female patients, based on the combination of two antihypertensive drugs, being ARB-II, the most used agent in combinations.

Key words: Arterial. Antihypertensive. Combination therapy. Pressure. Therapy.

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INTRODUCTION

High blood pressure (HBP) is the most frequent cardiovascular pathology with greater impact, because it causes 41% of mortality in elderly people in Lima[1]; likewise, it is the most frequent adjustable risk factor in cardiovascular events (CV)[2]. The main tests have conclusively shown that there is a direct relation between blood pressure level (BP) and cardiovascular morbimortality[3].

Its prevalence in Peru has increased from 23.7% to 27.3%, according to the TORNASOL II study done in 2011 nationwide. The greater part of population with HBP does not have treatment, or has an inappropriate one. According to the above mentioned study, 39.3% of hypertensive people had treatment, and only 20.6% of these ones have been controlled[4].

Changes of lifestyle are essential and strategic in prevention and treatment of HBP. So that, it must be a constant in every therapeutic scheme, regardless the need of using drugs. There are proved behaviors which, besides reducing effectively BP levels, also have positive impact on the decrease of CV events[5].

Regarding pharmacological therapy, the early taking of antihypertensive drugs (A-HBP) is recommended to people with levels of systolic blood pressure (SBP) ≥160 mmHg, or diastolic blood pressure (DBP) ≥100 mmHg, with any level of cardiovascular risk (CVR)[6-8]. The main benefits of A-HBP therapy are due to the reduction of BP and are independent of the drug chosen[9]. Therapy goals should be gradually reached in the first month after starting the treatment[10]. The use of combination therapy could be considered as an initial scheme in patients with basal BP significantly high o with high CVR[2].

In order to classify hypertensive patients as controlled, the choice is the clinical measurement of BP. It is recommended to achieve a clinical BP <140/90 mmHg in most of hypertensive populations [5,12-17]. Recently complementary methods have been recommended to verify the control of HBP; one of these ones is the Ambulatory blood pressure monitoring (ABPM), which has the advantage of being correlated more precisely with DOB than with clinical BP and even has greater prognostic value of events and CV mortality[18-20]. It is considered as controlled when having an average daytime SBP <135 mmHg and DBP <85 mmHg, night SBP <120 mmHg and DBP <70 mmHg, and 24-hour SBP <130 mmHg and DBP <80 mmHg[21].

Nowadays, local data, regarding the number of A-HBP agents and the type of combinations of these ones necessary to achieve the goals of HBP control, are not available here; that is the reason of this study, with which we pretend to describe the A-HBP treatment making emphasis on combination therapy in controlled hypertensive patients.

MATERIALS AND METHODS

This is a descriptive, observational and retrospective study. Medical records from the registry of patients of the Cardiology Procedures Office in the *Clinica Internacional* – based in *San Borja (Lima, Peru)* were reviewed, in order to make an ABPM between January 01st, 2013 and January 31st, 2014 (13 months). Inclusion criteria were: patients aged 18 or more years old; patients diagnosed with primary HBP: patients without any change in antihypertensive treatment during the month before the ABPM; patients ideally controlled according to ABPM criteria (daytime and night), patients with ABPM, with ≥70% of valid readings. The following were excluded: patients with secondary HBP; pregnant and postpartum patients; patients who were hospitalized in the last 30 days; patients with non-controlled endocrinopathies, chronic kidney disease (stage III and more), connective tissue disease (or any others requiring chronic corticotherapy), clinically significant cardiac arrhythmias or use of pacemakers, coronary disease, stroke, non-controlled psychiatric disorders.

Information of interest was registered out of reviewing medical records, the data recorded in the consultation nearest to the ABPM date. Besides age and gender data, clinical information such as weight, Body Mass Index (BMI), time of HBP and comorbidities, was obtained. When there was no record of the time of disease, the minimum time of disease was considered, from the first consultation where the HBP diagnosis was recorded and

background of this disease was indicated. Regarding auxiliary examinations, results such as total cholesterol, HDL, LDL, triglycerides and their date of taking, were registered. As far as the A-HBP treatment, the number of drugs, dosage and the starting date of schemes were registered, considering as reference the ABPM date. Additionally, the use of other non-A-HBP drugs was registered.

Regarding the ABPM, models 90217 or 90207 of SPACELABS, internationally recognised[20], were used. It was considered the execution date; average daytime, night and 24-hour SBP and DBP; night-time pattern data and the percentage of valid readings. The ABPM data of night-time pattern considered the following categories: *non-dipper*, if the decrease of night BP was lower than 10%; *dipper*, if the decrease was between 10% and 20%; extreme *dipper*, if the decrease was higher than 20%; and *riser*, when there was an increase.

The information was input in an electronic form with in-house validation applicable to mobile devices designed in the Magpi program. The data input was in charge of three researchers and a double review of selected medical records was carried out for quality control. The database was transferred to the Stata Program, version 12.0, for Mac software.

For the analysis, demographic and clinical characteristics according to gender were described. The value "p" was found for each variable. The drug or group of drugs more frequently used, both for the group of monotherapy and for that one of combination therapy, was identified, and it was described according to the gender, as well as to the tendency in night-time pattern, according to the group of treatment.

The Score de Framingham (SF) of 2008 was calculated in patients who had lipid profile, and the average daytime SBP was used instead of the clinical SBP. In case of patients who did not have the information of tobacco registered on their medical record, they were considered negative.

RESULTS

According to the inclusion and exclusion criteria of 1,007 medical records reviewed, 75 patients were selected (Figure 1).

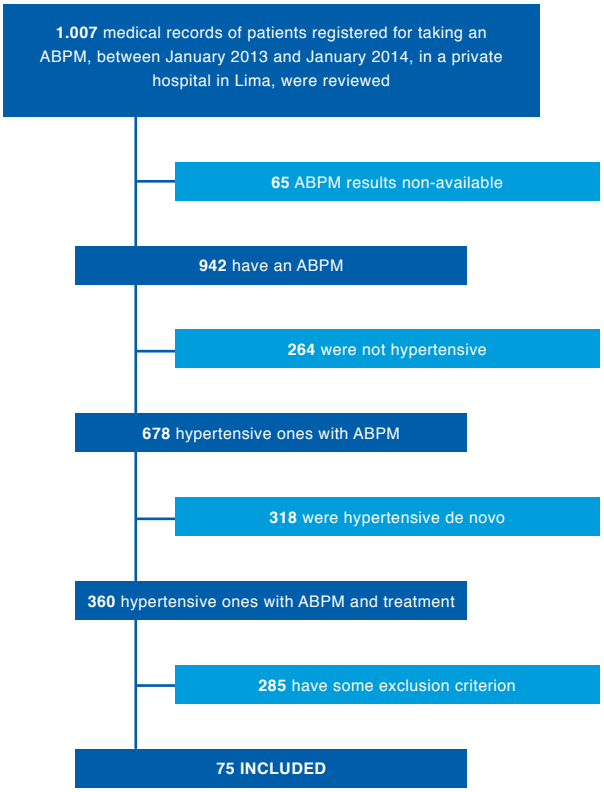

Figure 1. Process for identifying the study population.

As far as demographic features (Table 1), 48 out of 75 patients (64%) were women (the ratio of women to men was 1 to 8) and the average age was 59.5 years (standard deviation [SD] 13.2), women 62.5 (SD: 12) and men 54.2 (SD: 13.7) with $p < 0.05$. As far as clinical features (Table 1), the median diagnosis time of HBP was around of 4 years (49 months ± 43, information available in 58 cases). The BMI could be established in 44 cases with an average of 28.7 ± 4.2, and from these ones, 8 presented an ideal BMI, 22 overweight and 14 obesity.

One comorbidity was identified in 53 patients (71%) at least, and 12 out of 53 patients had more than one. The main comorbidities were: dyslipidemia (57%) and obesity (33%).

An average SF -of 2008- of 9.3% (SD: 7.1%) in global was found, which was greater for the group of

men (13%) (SD: 9.9%) than for women (7.3%) (SD: 3.8%). The SF for the 6 men taking acetylsalicylic acid (ASA) was between 1% and 30%, and for the 9 women between 1% and 15.9%.

The ABPM results are detailed in Table 2, the average daytime and night DBP were significantly lower in women (p <0.05). There was no statistical difference for DBP averages. As far as night-time patterns, about a half of the sample had a pattern different to *dipper* (48%), which represented a greater proportion for the group of women (52%) than for men (41%), p=0.35.

The median time between the beginning of the A-HBP treatment and execution of the ABPM was 7.2 months (interquartile range –IQR-): 1.9-19); in the group with combination therapy (median: 11.7 months, IQR: 4.3-23.6) grater than the group with monotherapy (median: 4.7 months, IQR: 1.6-16). Significant differences were observed for the averages of SBP and DBP (daytime and night), which were lower in the group of combination therapy. It was observed that most of the patients with *dipper* night-time pattern received monotherapy (60%), but most of the patients with combination therapy had a night pattern different to *dipper* (57%).

Table 1. Distribution of demographic and clinical characteristics according to gender.

Characteristics Number (%)	Women n=48	Men n=27	Global n = 75	p
Age (years old)	62.5 ± 12	54.2 ± 13.7	59.5 ± 13.2	0.01*
Time of disease (months)	52 ± 46.3	43 ± 37	49 ± 43	0.4**
Weight (kilogrames) (n=66)	69.6 ± 12.7	83.4 ± 9	74.3 ± 13.2	<0.001*
BMI (44)	28.8 ± 4.8	28.4 ± 2.8	28.7 ± 4.2	0.7*
Nº patients with BMI	28 (58%)	16 (59%)	44 (59%)	0.46***
Ideal weight	7 (15%)	1 (4%)	8 (11%)	
Overweight	11 (23%)	11 (41%)	22 (29%)	
Obesity[a]	10 (21%)	4 (15%)	14 (19%)	
No data available	20 (42%)	11 (41%)	31 (41%)	
Comorbidities				
Dyslipidemia	25 (52%)	18 (67%)	43 (57%)	0.22***
Obesity[a]	11 (38%) (n = 29)	4 (27%) (n = 16)	15 (33%) (n = 45)	0.44***
Hypothyroidism	5 (10%)	0	5 (7%)	-
Diabetes	3 (6%)	1 (4%)	4 (5%)	NS****
Other	1 (2%)	2 (8%)	3 (4%)	

T test, **Mann-Whitney test, * Chi-square test, **** Fisher's exact test. BMI (body mass index). Based on the total number of patients with available BMI. (a) Based on patients with available BMI plus patients diagnosed with obesity without BMI available. Other: peripheral arterial disease, chronic kidney disease.*

Combination therapy was prescribed for 35 patients (47%) (Table 2). As for predominance of the type of treatment according to gender, 58% of women received combination therapy whereas 74% of men received monotherapy, p <0.01.

Features according type of therapy are detailed in Table 3. Age and time of disease were greater in the group who received combination therapy, with p=0.02 in both cases. The group of combination therapy showed greater proportion of dyslipidemia (69%) and obesity (23%) in comparison to the group with monotherapy (48% and 18%).

A-HBP families most commonly indicated in the group who received monotherapy were: angiotensin II receptor blocker (ARB-II) (58%). In the group of combination therapy the average of A-HBP was 2.4, predominant schemes were: ARB-II + hydrochlorothiazide (HCT) (51%), ARB-II + HCT + calcium channel blocker (CCB) (17%); additional results are detailed in Tables 4 and 5.

Polypharmacy was observed in 36 patients (48%) considering A-HBP and non- A-HBP drugs. The rate with polypharmacy was higher in the group with comorbidities (58% vs. 17%, p=0.01). The most frequent non-A-HBP drugs were hypolipidemic drugs (27/43 patients with dyslipidemia), among them: atorvastatin, used by 19 patients out of a total of 27 (70%), and ASA in 15 patients out of a total of 75 patients (20%) (Table 7).

Table 2. ABPM Values and distribution of night-time pattern by gender.

ABPM		Women n=48	Men n = 27	Global n = 75	p
Day	Systolic	117 ± 8	120 ± 9	118 ± 9	0.08*
	Diastolic	70 ± 7	74 ± 6	71 ± 6	0.02*
Night	Systolic	104 ± 8	107 ± 6	105 ± 8	0.2*
	Diastolic	60 ± 6	63 ± 4	61 ± 5	0.03*
24h	Systolic	113 ± 7	117 ± 7	115 ± 7	0.05*
	Diastolic	67 ± 6	71 ± 5	69 ± 6	0.01*
Night-time	Dipper	23 (48%)	16 (59%)	39 (52%)	
pattern	Other	25 (52%)	11 (41%)	36 (48%)	0.35*

**T test.*
Other: Non-dipper, Extreme Dipper, Riser

Table 3. Type of therapy and number of antihypertensive drugs according to gender.

Therapy		Female n = 48 (%)	Male n = 27 (%)	Global n=75 (%)
Monotherapy		20 (42%)	20 (74%)	40 (53%)
Combination therapy	Total	28 (58%)	7 (26%)	35 (47%)
	2	18 (37%)	4 (15%)	22 (30%)
	3	9 (19%)	3 (11%)	12 (16%)
	4	1 (2%)	-	1 (1%)
Antihypertensive median (average)		2 (1.8)	1 (1.4)	1 (1.7)

Table 4. Distribution of demographic and clinical characteristics according to type of therapy.

Characteristics Number (%)		Monotherapy n = 40	Combination therapy n = 35	Global n = 75	p
Gender					
Female		20 (50%)	28 (80%)	48	
Male		20 (50%)	7 (20%)	27	0.007***
Age (years old)		56.2 ± 12.9	63.2 ± 12.6	59.5 ± 13.2	0.02**
Time of disease (months)		39 ± 37	61.5 ± 47.4	49 ± 43	0.02**
Time of treatment (months)		4.7 [RIC: 1.6-16]	11.7 [RIC: 4.3-23.6]	7.2 [RIC: 1.9-19]	
Weight (kilogrames)		76.1 ± 12.7	72.6 ± 13.7	74.3 ± 13.2	
Overweight		13 (33%)	10 (29%)	23 (32%)	0.3**
Comorbidities					0.29***
Dyslipidemia		19 (48%)	24 (69%)	43 (57%)	
Obesity		7 (32%) (n = 22)	8 (35%) (n = 23)	15 (33%) (n = 45)	0.03***
Hypothyroidism		2 (5%)	3 (9%)	5 (7%)	0.6***
Diabetes		2 (5%)	2 (6%)	4 (5%)	-
Other		1 (3%)	2 (6%)	3 (4%)	NS****
ABPM					
Day	Systolic	120 ± 9	116 ± 8	118 ± 9	
	Diastolic	73 ± 6	70 ± 7	71 ± 6	0.04*
Night	Systolic	107 ± 6	103 ± 7	105 ± 8	0.02*
	Diastolic	63 ± 4	60 ± 6	61 ± 5	0.02*
24h	Systolic	116 ± 7	113 ± 7	115 ± 7	0.02*
	Diastolic	70 ± 5	67 ± 7	69 ± 6	0.05*
Night-time Pattern	Dipper	24 (60%)	15 (43%)	39 (52%)	0.03*
	Other	16 (40%)	20 (57%)	36 (48%)	0.14***

T test, ** Mann-Whitney test, * Chi-square test, **** Fisher's exact test. Othes: Non-dipper, Extreme Dipper, Riser.*

Table 5. Frequency of combinations of antihypertensive families prescribed matching the ABPM.

Combinations of antihypertensive families	Female (%)	Male (%)	n (%)
ARB-II + HCT	14 (50%)	4 (57%)	18 (51%)
ARB-II + HCT + CCB	5 (18%)	1 (14%)	6 (17%)
ARB-II + HCT + BB	2 (7%)	1 (14%)	3 (9%)
ARB-II + CCB	2 (7%)	-	2 (6%)
ARB-II + BB	1 (4%)	-	1 (3%)
ARB-II + BB + ACEI	1 (4%)	1 (14%)	2 (6%)
ACEI + BB	1 (4%)	-	1 (3%)
ACEI + HCT + BB	1 (4%)	-	1 (3%)
ARB-II + CCB + BB + S	1 (4%)	-	1 (3%)

Angiotensin II receptor blocker (ARB), hydrochlorothiazide (HCT), calcium channel blocker (CCB), beta-blocker (BB), angiotensin-converting enzyme (ACE) inhibitors, Spironolactone (S).

Table 6. Frequency of use of antihypertensive drugs by families in patients receiving monotherapy when applying the ABPM.

Families of Antihypertensive drugs	Female (%)	Male (%)	n (%)
ARB-II	10 (50%)	13 (65%)	23 (58%)
ACEI	3 (15%)	4 (20%)	7 (18%)
BB	3 (15%)	3 (15%)	6 (15%)
CCB	3 (15%)	-	3 (8%)
AA	1 (5%)	-	1 (1%)

Angiotensin II receptor blocker (ARB), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blocker (CCB), beta-blocker (BB), alpha- agonist (AA).

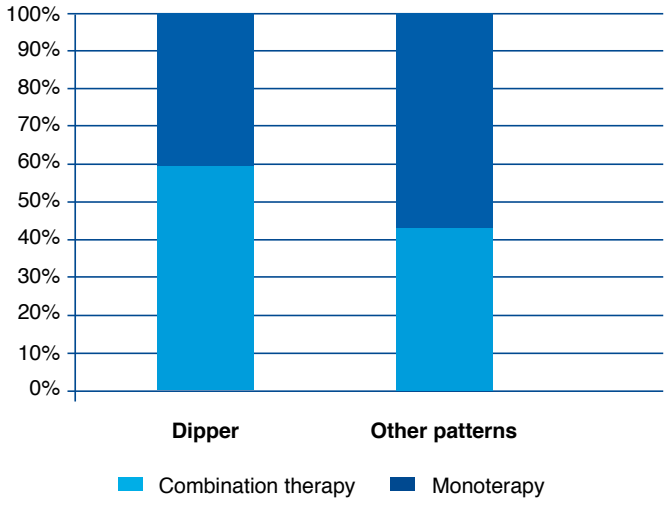

Figure 2. Frequency of night-time pattern by type of therapy. Other patterns: Non-dipper, extreme dipper, Riser

Table 7. Frequency of non-antihypertensive treatment according to type of antihypertensive therapy.

Non-antihypertensive drugs	Monotherapy n = 40	Combination therapy n = 35	Global n = 75
Lipid lowering drugs			
Global	13 (33%)	14 (40%)	27 (36%)
Atorvastatin	7 (18%)	12 (34%)	19 (25%)
Simvastatin	3 (7%)	1 (3%)	4 (5%)
Ciprofibrate	1 (3%)	1 (3%)	2 (3%)
Gemfibrozil	2 (5%)	-	2 (3%)
Ezetimibe	3 (7%)	-	3 (4%)
Antiplatelet drugs			
AAS	5 (13%)	10 (29%)	15 (20%)
Clopidogrel	-	1 (3%)	1 (1%)
Antidiabetic drugs			
Metformina	4 (10%)	1 (3%)	5 (7%)
Thyroid hormones			
Levothyroxine	2 (5%)	3 (9%)	5 (7%)

DISCUSSION

Hypertension is a serious condition that carries a high CVR, globally associated to a high rate of morbidity and mortality. Success of hypertension treatment is limited despite the different approaches to diagnosis and treatment[1], since at population level, less than a half of hypertensive patients are controlled[4].

This study presents clinical characteristics, with emphasis on the therapy received by a sample of controlled hypertensive patients, confirmed by ABPM.

In this sample there were more women with an average age significantly higher than men. Although in our country there is higher prevalence of hypertensive male patients[22], this finding is expected since it is recognized that women go more frequently to the doctor and the number of consultations in hypertensive women is three times the number for men[1]. In addition, the average age for women was higher probably due to the increased incidence of HBP in postmenopausal women[22].

A proportion of the chosen population can be considered from moderate to high CVR according to the following factors: average age (nearly 60 years old), overweight or obesity, dyslipidemia and SF. Furthermore, a pathological night-time pattern in about half of the

sample is a predictive factor of CV and DOB events[23]. Then it is outstanding to find an average short time of disease, being it underestimated probably because it is a largely asymptomatic disease with delayed diagnosis.

Obesity has been considered an epidemic[24], and its relation with hypertension is recognized. In the Framingham study it was observed that SBP and DBP increased directly with the BMI[25], and in PRESCAP studies it was observed that excessive weight is one of the variables associated with poor control of BP[26], explained by the increase of insulin resistance in these patients, also increasing CVR[25]. In this sample, despite reporting a bias, it is estimated 32% of obese people, similar to hypertensive population reported by a study conducted in Spain where 36% is reported[27].

Dyslipidemia is considered a CVR factor, since it causes endothelial damage[28], classically it is recognized that increased LDL, decreased HDL and increased triglycerides are independent risk factors[29]. In this study, various combinations of dyslipidemias for most of the patients in the sample were recorded.

It was observed that the sample profile consisted of patients with significant percentages of obesity and dyslipidemia. For this reason, the SF was calculated, finding an average value of 9.3%. It is important to notice that there were biases in calculation, such as the BP value used (daytime SBP according to the ABPM in place of clinical BP), the observation that patients were non-smokers and that some of them were receiving lipid-lowering therapy, which altered lipid profile underestimating the average SF.

Hypertension is related to the use of various pharmacological groups -in addition to the antihypertensive ones- such as lipid-lowering drugs and ASA, which was reflected in the higher proportion of polypharmacy in patients with comorbidities.

The use of ASA for primary prevention in patients with SF ≥10% (men) and ≥20% (women) is recommended[15,30]; however, more recent studies suggest that more researches are required in this regard, since the risk and benefit of its use is not determined[2]. In most of male patients receiving ASA, it was properly indicated, unlike prescription for women, who did not reach the minimum SF. For these cases actual SF calculation is required in order to establish an appropriate indication.

In the group of patients with dyslipidemia, atorvastatin was the most commonly prescribed lipid-lowering drug. This was an expected finding since efficacy and safety of statin are known and it has been validated by the ASCOT-LLA study. The same study showed that high-risk patients are benefited of statins as primary prevention[31].

Combination therapy, according to guidelines for hypertension is recommended in patients with high CVR and/or basal BP ≥160/100 mmHg, being the latter the best indicator for prescription[10]. This is because patients with such characteristics tend to have a difficult BP control and often require the association of antihypertensive drugs. As previously mentioned, combination therapy has the advantage of being more likely to achieve BP goals and of doing it in less time[19].

The use of combination therapy in hypertensive population occurs in about 14% according to the PURE study[32]. In this study sample, most of the women received combination therapy, unlike men who mostly received monotherapy. In general, it was found that about a half of them used combination therapy. The most frequently used scheme was formed by two drugs, followed by one of three drugs. Furthermore, the time of disease was significantly higher and a higher percentage of dyslipidemia was found in patients with combination therapy. These features are expected because the longer the disease, older age and more comorbidities, the greater difficulty in control with monotherapy[8], making convenient the use of a combined scheme. Despite this, a half of the sample was controlled with monotherapy, who were younger, shorter time of disease and lower percentage of dyslipidemia, being all these differences statistically significant between both therapy groups.

The family of drugs most frequently used in this sample, both for monotherapy and combination therapy, were ARBs-II. HBP physiopathology reinforces that this disease requires the use of a blocker of the renin-angiotensin-aldosterone system (RAAS)[5], and this finding may be because there is no inferiority shown

for preventing CV events or mortality between these two groups[33], However, benefits of ARBs-II are having less side effects, high tolerability and greater stability at pharmacodynamics, so that they are prescribed for once a day; features that enhance adherence[11,21]. In *TORNASOL II* study, it was found that ACE Inhibitors were predominantly used4. The difference of choice between these families may be due to different acquisitive levels of the samples studied since ACE Inhibitors have lower cost.

The most commonly used schemes of combination therapy were: ARB-II + HCT followed by ARB-II + HCT + CCB. This is consistent with international recommendations on choosing ARBs-II together with HCT as first line for patients with high CVR[5]. As for HCT, its impact on morbidity and mortality was shown several decades ago[34]. Regarding the combination of ARB-II with CCB, it has been more recently released showing advantages on which the ACCOMPLISH study demonstrated superiority for the combination of ARB-II + HCT in reducing CV events in patients with high CVR[35]. Despite this, possible explanations for the prevalence of HCT prescription are the impact of pharmaceutical industry on its availability in healthcare centers and the greater accessibility in comparison to CCB.

As for the triple combination, it is recognized that this is reserved for patients who do not reach an adequate BP reduction. This is consistent with the use of that scheme in this study. The TRINITY study demonstrated the greater effectiveness of these triple schemes for difficult BP control[36].

SBP and DBP (daytime and night) averages were lower in patients with combination therapy; although this result was expected because by using two drugs their actions are potentiated producing greater BP lowering, it is not determined the lowest BP goal, since in patients with high RCV increases the frequency of ACV and IMA with an office DBP <70 mmHg[37].

Among limitations it should be emphasized that this study is based on a non-significantly representative sample of general population, since it is comprised of patients attended in a private healthcare center, with better access to specialized cardiology services. It is also recognized that in these centers pharmaceutical industry has greater impact on prescription of certain drugs, which could also influence the results. Being a retrospective study, various types of biases were presented, particularly information and registration. However, it is the first local study about it opening a number of questions that need to be verified with further studies.

Finally, despite of being a sample of patients with controlled hypertension, there are several important points to discuss on the indicated therapy, since in a significant proportion of patients with high CVR, a combination therapy had to be applied. Furthermore, the use of ASA as primary prevention is only indicated in patients with high CVR, so it should be evaluated the benefit-risk of its prescription. Similarly, it is important that physicians emphasize the need to change lifestyles for a better control of hypertension and reduction of CVR. Finally, an ABPM control is recommended in elderly patients with high CVR to discard hypotensive episodes, which would increase the risk of CV events.

GRANTS OR FUNDING RESOURCES

None.

CONFLICTS OF INTEREST

The authors report no conflict of interest regarding this manuscript.

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