Combination of Amlodipine and Enalapril in Hypertensive Patients with Coronary Disease

Marcos Rienzo[1], José Francisco Kerr Saraiva[2], Paulo Roberto Nogueira[3], Everli Pinheiro de Souza Gonçalves Gomes[1], Miguel Antonio Moretti[1], João Fernando Monteiro Ferreira[1], Dikran Armagnajian[4], Antonio de Pádua Mansur[1], José Antonio Franchini Ramires[1], Luiz Antonio Machado César[1]

Department of Cardiopneumology of Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (USP)[1], São Paulo, SP, Faculdade de Medicina da Pontifícia Universidade Católica de Campinas[2], Campinas, SP, Instituto de Moléstia Cardiovasculares de São José do Rio Preto[3], São José do Rio Preto, SP, Instituto Dante Pazzanese de Cardiologia[4], São Paulo, SP - Brasil.

Summary

Background: Patients (pts) with stable coronary artery disease (CAD) can benefit from a decrease in the blood pressure (BP), according to recent studies.

Objective: To evaluate the efficacy and tolerability of the fixed combination: amlodipine + enalapril, when compared to amlodipine in the normalization of the diastolic arterial pressure (DAP) (≤85 mmHg), in pts with CAD and systemic arterial hypertension (SAH).

Methods: Double-blind and randomized study, with two groups of pts with DAP ≥90 and <110 mmHg and CAD. Patients with left ventricular ejection fraction (LVEF) < 40%, symptoms of heart failure or angina class III and IV, severe diseases and DAP ≥110 mmHg during the four-week wash-out with atenolol treatment alone, were excluded. After the wash-out, pts were randomly distributed for the use of the combination (A) or amlodipine (B) and were followed every four weeks up to 98 days. The initial doses (in mg) were, respectively: A- 2.5/10 and B- 2.5; the doses were increased when DAP > 85mmHg, at the visits. Statistical analysis was carried out with χ^2, Fischer and analysis of variance, for p< 0.05.

Results: Of the 110 selected pts, 72 (A= 32, B= 40) were randomized. The decreases in DAP and systolic arterial pressure (SAP) were significant (p< 0.01), but with no difference between the groups in mmHg: SAP, A (127.7 ± 13.4) and B (125.3 ± 12.6) (p= 0.45) and DAP, A (74.5 ± 6.7 mmHg) and B (75.5 ± 6.7 mmHg) (p= 0.32). Group A presented a lower incidence of lower-limb edema: (7.1% vs. 30.6%, p=0.02) on the 98th day of follow-up.

Conclusion: The fixed combination of enalapril and amlodipine, as well as isolated amlodipine, was effective in the normalization of BP in pts with CAD and SAH stages I and II, adding blockage of the renin-angiotensin system. (Arq Bras Cardiol 2009;92(3): 173-179)

Key words: amlodipine; enalapril; hypertension; coronary artery disease.

Introduction

The calcium-channel antagonists (ACa^{++}) and the angiotensin-I -converting enzyme inhibitor (ACEI) are among the preferred antihypertensive drugs for the treatment of arterial hypertension in patients with coronary artery disease (CAD), because they protect the target-organs with low incidence of adverse reactions[1-3].

They have a slight influence on the metabolic profile and prevent trophic phenomena, such as left ventricular muscular hypertrophy and vascular hypertrophy[4]. The ACEI promote the decrease in coronary events after myocardial infarction, in ischemic myocardiopathy[5], and, in recent years, the HOPE[6] and EUROPA[7] studies have demonstrated a decrease in cardiovascular events in patients with stable CAD, especially diabetic ones. On the other hand, the dihydropyridinic calcium antagonists promote important arterial vasodilation and are also broadly used as anti-angina therapy.

When dealing with hypertensive patients with CAD, the dihydropyridinic derivatives are an important option[8,9]. The main adverse reactions of these anti-hypertensive drugs are: ACEI-induced coughing[10] and lower-limb edema induced by ACa^{++}. The lower-limb edema that can occur with the use of dihydropyridinic calcium antagonists results from a lower arteriovenous pressure gradient in blood capillaries[11]. This type of edema in general does not respond to diuretics. To reduce the edema, the ACEI are frequently associated, which promote venodilation. Therefore, the association of ACEI and ACa^{++} can result in better pressure control with less lower-limb edema[12], *considering the onset of coughing*. The present study aimed at evaluating the efficacy and tolerability of the amlodipine-enalapril combination (SINERGEN™) in a fixed dose, using a single galenic formulation, compared to amlodipine in the control of the arterial pressure of hypertensive patients with stable CAD.

Mailing address: Luiz Antônio Machado César •
Rua Constantino de Souza, 1580 - Campo Belo - 04605-004 - São Paulo, SP - Brazil
E-mail: lucesar@cardiol.br, dcllucesar@incor.usp.br
Manuscript received March 28, 2008; revised manuscript received May 19, 2008; accepted June 12, 2008.

Patients and methods

This was a phase-IV, randomized, multicentric and double-blind study, carried out between January 2002 and September 2005. The study was approved by the Ethics Committee of all the participating Institutions and the selected patients signed the Free and Informed Consent Form.

Inclusion criteria

History of stages I and II SAH (90mmHg ≤ diastolic arterial pressure (DAP) < 110mmHg) using only betablocker at the moment of randomization; aged 21 to 80 years; CAD confirmed by coronary angiography, disclosing the involvement of at least 50% of lumen reduction in one of the main branches in its proximal or mid-third and history of stable angina.

Exclusion criteria

Pregnancy or non-use of positively effective contraceptive methods; stage III or malignant SAH; DAP ≥ 110mmHg at any moment during the wash-out period; left ventricular systolic dysfunction with left ventricular ejection fraction (LVEF) ≤40%, measured at the transthoracic echocardiogram; congestive heart failure (CHF); NY Heart Association[13]; Canadian Cardiovascular Society Functional Class III or IV angina pectoris[14]; unstable myocardial ischemic syndrome in the last six months; chronic renal failure with creatinine >2.0mg/dl; active or end-stage liver disease; hyper (>5,5mEq/l) or hypokalemia (<3.5 mEq/l); neoplasias undergoing treatment; evident blood dyscrasias; left branch block at the electrocardiogram (ECG) or other situations that prevented the analysis of the ST-segment during stress; concomitant use of medications that could interfere with the study medication; previous history of therapeutic failure with the study medications; use of alpha-blocker for benign prostate hyperplasia; BMI > 35kg/m^2; and having participated in any other clinical trial in the last thirty days before enrolment in this study.

Study design

After the wash-out period of 21 days, during which the patients were seen weekly and during which they remained without the previously prescribed anti-hypertensive medications, except atenolol, these were randomized in two groups. Group A received the fixed amlodipine-enalapril combination and Group B received only amlodipine for 98 days. During the follow-up, the patients were seen four times by the physicians and three BP measurements in the supine and orthostatic positions were carried out in each visit, with a *Tycos* Welch Allyn® aneroid sphygmomanometer (Skaneateles Falls, NY, USA), using a number 11 adult cuff, calibrated and gauged annually by INMETRO. The systolic and diastolic values were considered when the first and fifth phases of Korotkoff's sounds were heard, during auscultatory determination[15]. Each measurement was performed after rest of at least 5 minutes in each of the positions and with more than 1 minute of difference between each measurement; for accuracy, the lowest DAP value obtained was considered.

Dose adjustment

The medication doses were increased when DAP was ≥ 85 mmHg. In Group A, the fixed doses were, respectively: amlodipine 2.5 mg + enalapril 10 mg, amlodipine 5mg + enalapril 10mg and amlodipine 5mg + enalapril 20mg. In Group B, the doses were, respectively: amlodipine 2.5mg, 5mg, or 10mg, in a single daily dose for both groups. Hydrochlorothiazide 12.5 mg/day was associated to reduce DAP when maximum doses were being administered, at the last but one medical visit of the study. At the randomization and last visit of the study period, all patients were submitted to a 12-derivation ECG and laboratory analysis.

Statistical methods

The data of the initial evaluation, efficacy and safety were summarized by descriptive statistics per treatment group, considering the intention-to-treat analysis. The anti-hypertensive efficacy was evaluated considering:

a) Percentage of patients that, at the end of the study, presented diastolic pressure levels ≤ 85 mmHg in the supine position (Criterion 1);

b) To this percentage, we added the percentage of patients that, although did not have the BP normalized according to the above criteria, achieved at the end of the study a decrease in the diastolic pressure ≥ 10 mmHg in the supine position (Criterion 2).

The study groups were compared by the Chi-square test or Fisher exact test regarding the qualitative variables, whereas the quantitative variables were compared by analysis of variance for repeated measures. The level of significance was set at 0.05 (alpha=5%).

Results

Seventy-two patients were randomized, from a total of 110 selected patients. Among the 38 patients that were not included during the selection period, 36 were excluded due to protocol violation and one was excluded due to lack of adherence during the wash-out period (Figure 1). The initial clinical characteristics of the patients can be found in Table 1. It was observed in Group A, a higher prevalence of diabetes mellitus (6.3% *vs*. 0%; p=0.04) and dyslipidemia (65.6% *vs*. 42.5%; p= 0.05). During the follow-up, four patients were excluded from the study due to adverse events, being one in Group A and 3 in Group B, and subsequently, four more due to lack of adherence to treatment (3 in A and 1 in B).

After the 98 days, there were no significant differences between Groups A and B in relation to criteria 1 and 2 of effectiveness for the systolic (127.7 ± 13.4 *vs*. 125.3 ± 12.6 mmHg; p= 0.45) and diastolic (74.5 ± 6.7 *vs*. 75.5 ± 6.7 mmHg; p= 0.32) pressures (Figures 2 e 3), as well as for heart rate. Considering the criterion 1, 30 patients (93.8%) in A and 38 (95%) in B met the criterion. Regarding criterion 2, that occurred in 31 and in 39 patients (96.9% and 97.5%), respectively in groups A and B. (p=1.00 for both ambos criteria).

During evolution, adverse events were observed and are shown per patients in Table 2, without statistically significant

differences in the total, although there was a higher incidence of coughing I group A (6.2% vs. 2.5%, p= 0.58). However, at the end of the 14 weeks, we observed a higher incidence of lower-limb edema in group B (7.1% *vs*. 30.6%; p= 0.02) (Table 3); the same had been observed on the 10th week (10% vs. 30.6%; p= 0.04), although there were no statistically significant differences in the other visits. It was also observed a decrease in the number of patients undergoing follow-up at each visit. Regarding the frequency of anti-hypertensive dose-adjustment necessity, there was no difference between the groups and the mean daily dose of amlodipine was higher in the group receiving amlodipine alone (3.8 *vs*. 5.6 mg). The same occurred when we assessed the need to add hydrochlorothiazide in 5 (17.9%) patients in Group A and in 6 patients (20.0%) in Group B. No deaths occurred up to the 14th week of the study.

Discussion

In the present study, we observed a mean decrease in SAP of 20 mmHg in Group A (enalapril + amlodipine), from 145.1 to 124.7 mmHg and of 27 mmHg in Group B (amlodipine), from 152.8 to 125.3 mmHg. Although the decrease was higher in Group B, the values were close at the end of the study (124.7 *vs*. 125.3 mmHg) and below 130 mmHg, as required and proposed by our directives[15]. As for the mean DAP decrease, we observed, in both groups, a reduction of 19 mmHg. The mean daily dose of amlodipine used was higher in the group that received amlodipine alone (3.8 *vs*. 5.6 mg), demonstrating that the association of enalapril indeed caused the addition of an anti-hypertensive effect in the patients from Group A. That can also explain the lower incidence of lower-limb edema in the group receiving the combined therapy, as observed, as the lower dose of amlodipine and the arterial vasodilating effect as well as the venous vasodilating effect of the ACEI resulted in the lower incidence of edema. On the other hand, one must consider the importance of blocking the renin-angiotensin-aldosterone system, with benefits that go beyond the arterial pressure decrease and especially in high-risk populations, such as in patients with CAD. Therefore,

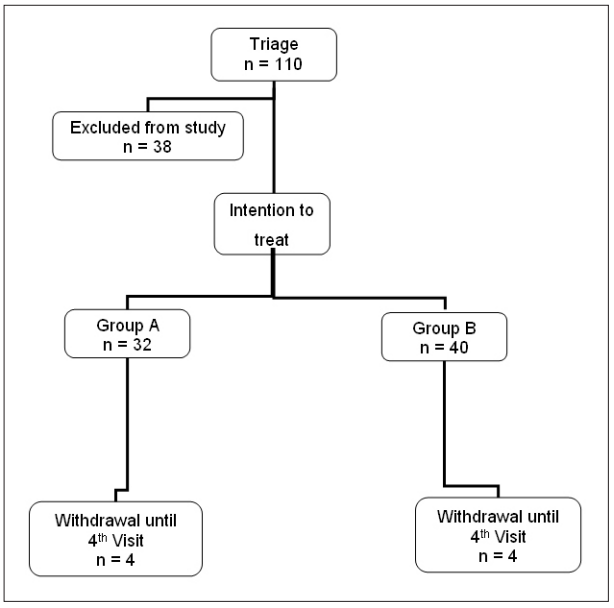

Figure 1 - Study organization chart, starting from patient selection, at the several visits and the withdrawals along time.

Table 1 - Initial characteristics of the group at the moment of randomization

	Group A (n= 32)	Group B (n=40)	P
	in %		
Male sex	71.9	70.0	0.86
Smoking	12.5	30.0	0.08
Alcohol consumption	6.3	5.0	1.00
Physical Activity	50.0	37.5	0.29
Dyslipidemia	65.6	42.5	0.05
Diabetes	6.3	0.0	0.04
Obesity, with BMI ≥30.0	0.0	2.5	0.99
Stage II SAH	56.3	62.5	0.59
	in means ± SD*		
Age (years)	60.8 ± 8.5	60.4 ± 7.9	0.82
Time of SAH† (yrs)	10.8 ± 8.3	11.8 ± 8.5	0.55
Time of CAD‡ (yrs)	4.0 ± 3.2	4.6 ± 3.7	0.61
SAP§ supine (mmHg)	145.1 ± 10.8	152.8 ± 13.2	0.07
DAP// supine (mmHg)	93.8 ± 3.1	94.5 ± 3.1	0.08
BMI¶ (kg/m²)	27.2 ± 3.4	27.7 ± 3.2	0.56

** Standard deviation, † systemic arterial hypertension, ‡ coronary artery disease, § systolic arterial pressure, // diastolic arterial pressure, ¶ body mass index.*

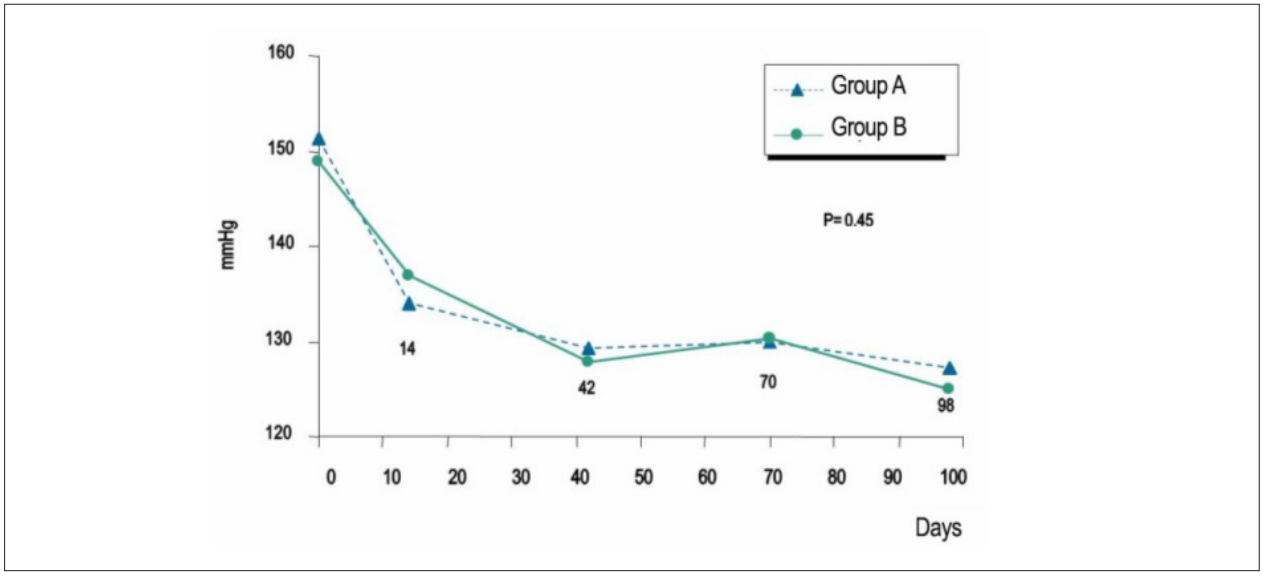

Figure 2 - Systolic arterial pressure means, in the supine position, in Groups A (combined therapy) and B (amlodipine) throughout the study period.

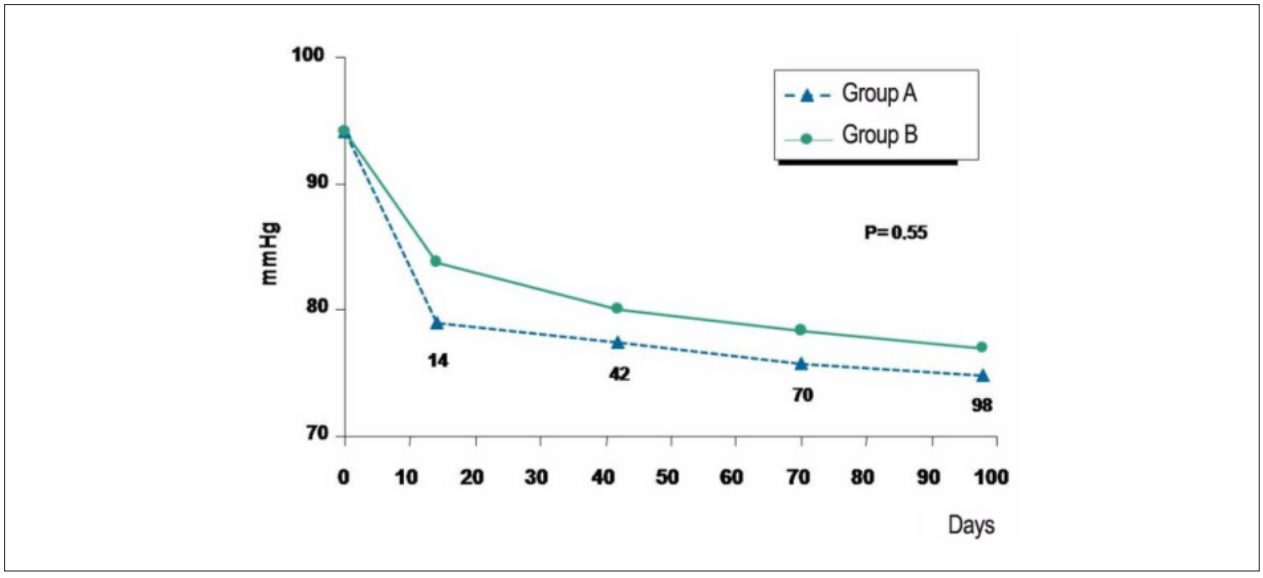

Figure 3 - Diastolic arterial pressure means, in the supine position, in Groups A (combined therapy) and B (amlodipine) throughout the study period.

these results must be understood within the current setting of SAH treatment possibilities.

It is known that the risk of cardiovascular diseases in hypertensive patients is reduced with the effective treatment of SAH. The decrease in the cardiovascular morbimortality observed in the last 50 years can be mostly attributed to a broader availability and use of anti-hypertensive drugs. Randomized studies evaluated in meta-analysis have shown that the decrease in BP results in rapid reductions in cardiovascular risk[16]. For instance, a decrease of 10 mmHg in SAP or 5 mmHg in DAP can correspond to a 50 or 60% reduction in the risk of death by cerebrovascular accident (CVA) and approximately 40 to 50% lower risk of death by CAD or other cardiovascular causes in middle-aged patients,

Table 2- Cumulative adverse events throughout the study

Adverse Events	Group A N (%)	Group B N (%)	Comparison P value
No	21 (60.7)	22 (65.0)	0.45
Yes	11 (39.3)	18 (45.0)	
Headache	2 (6.2)	2 (5.0)	
Edema	7 (12.5)	11 (22.5)	
Coughing	2 (6.2)	1 (2.5)	
Others	2 (6.2)	6 (15.0)	
Total	32 (100.0)	40 (100.0)	

Table 3 - **Presence of lower-limb edema in each follow-up visit**

Lower-limb edema	Group A n (%)	Group B n (%)	Comparison p value
Day 0	(n= 32)	(n= 40)	
Yes	1 (3.1)	2 (5.0)	1.00
No	31 (96.9)	38 (95.0)	
Day 14 – n (%)	(n = 32)	(n = 38)	
Yes	3 (9.4)	6 (15.4)	0.50
No	29 (90.6)	33 (84.6)	
Day 42	(n = 32)	(n = 38)	
Yes	6 (18.8)	5 (13.2)	0.52
No	26 (81.3)	33 (86.8)	
Day 70	(n = 30)	(n = 36)	
Yes	3 (10.0)	11 (30.6)	0.04
No	27 (90.0)	25 (69.4)	
Day 98	(n = 28)	(n = 36)	
Yes	2 (7.1)	11 (30.6)	0.02
No	26 (92,9)	25 (69,4)	

which can also be observed in elderly patients, however at a lower extent[17].

In patients older than 85 years, it has been observed that a decrease in BP reduces mortality by CVA; however, the same is not true regarding the mortality due to other cardiovascular causes[18]. A prospective study with 960,000 patients demonstrated that, considering the BP interval between 115x75 and 185x115 mmHg, for each 20 mmHg of SAP increase (or 10 mmHg of DAP increase), the risk of death by CAD or CVA practically doubles[19]. Our results show that the combined therapy was able to reduce the pressure levels to this ranges, to the point of providing, in theory, the same benefits observed in this meta-analysis[19]. It has also been established that betablockers are drugs of choice in the treatment of patients with CAD, with or without SAH. They have the capacity of improving ischemia and alleviate the angina through their negative inotropic and chronotropic effects. Additionally, they improve the coronary perfusion through the increase in the diastolic filling time generated by the decrease in heart rate and inhibit the release of renin by the juxtaglomerular apparatus. Thus, they are considered the basis of the treatment of patients with CAD[20], which was taken into account in our study.

Furthermore, the benefit of using ACEI in patients with CAD or in those individuals at high-risk for the development of cardiovascular diseases, has been largely established by several studies and among them, the SAVE[5], HOPE[6], and EUROPA[7] studies, which demonstrated a decrease in major cardiovascular events in this group of patients. This evidence makes the prescription of ACEI be at least class IIa, according to our directives[20], although it is already class Ia with level of evidence A in the European directive[21] for the treatment of patients with CAD and SAH. Thus, the use of an ACEI, as in the combined therapy used in the present study, brings additional benefits to the decrease in arterial pressure. On the other hand, considering the use of amlodipine in the CAMELOT[22] study, which compared enalapril or amlodipine to placebo in patients with CAD, of which 60% presented a history of hypertension, there was a lower frequency of cardiovascular events in the amlodipine group, including the decrease in the atherosclerosis progression in this group when compared to the others, which was demonstrated in the sub-study that evaluated the coronary disease through intravascular ultrasonography[23].

This shows that amlodipine is an interesting option for patients with CAD, as in addition to its marked BP-reducing properties, as demonstrated in the VALUE[24] study, which compared valsartan with amlodipine in more than 15,000 patients with SAH and high risk of cardiovascular events (46% of them had CAD), this drug also resulted in a lower incidence of AMI, although with a higher number of DM diagnosed during the 4.2-year follow-up period.

Finally, a systematized meta-analysis[25] aiming at evaluating the value of combined therapy in the treatment of SAH, after the analysis of 354 randomized treatment studies, showed some findings that are worth mentioning, as follows:

1) the decrease in BP, using half of the conventional dose of a certain drug, was only 20% less than that observed when the standard dose was used; however, the incidence of adverse events was much less frequent;

2) the efficacy of the combined therapy showed to be additive, but the prevalence of adverse events was different, being much lower; and

3) a combination of three drugs, at half their standard doses, considering the attained BP reduction, potentially decrease the risk of CVA in 63% and coronary events in 46% of the patients.

Conclusion

The fixed combination of enalapril and amlodipine (SINERGEN™), when compared to amlodipine alone in patients with CAD and stages I and II SAH is effective in reducing BP, with a lower incidence of adverse events, such as lower-limb edema, which can imply in better adherence to treatment, and, consequently, a decrease in the incidence of major cardiovascular events in this group of patients. Furthermore, the blocking of the renin-angiotensin-aldosterone system is important in these patients and must result in other benefits in addition to the BP decrease, which does not seem to occur with the isolated use of amlodipine. As a limitation to this conclusion, it is worth mentioning the small number of evaluated patients, but the study design allows us to show how effective the treatments were, under stringent follow-up.

Acknowledgements

This study had the financial support of Biosintética-Aché Laboratories and the participation of the following main investigators and respective centers:

Denilson Albuquerque – Universidade Estadual do Rio de Janeiro.

Dikran Armaganijan – Instituto Dante Pazzanese de Cardiologia.

Iran Castro - Instituto de Cardiologia de Porto Alegre.

José Francisco K. Saraiva - Pontifícia Universidade Católica de Campinas.

José Péricles Esteves - Hospital Português, Salvador.

Luiz A. M. César – national study coordinator– Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – Department of Cardiopneumology – (InCor), São Paulo.

Otávio R. Coelho – UNICAMP

Paulo Roberto Nogueira – Instituto de Moléstia Cardiovasculares de São José do Rio Preto.

Renato Vaz - Instituto de Cardiologia de Porto Alegre.

Potential Conflict of Interest

We declare potential conflict of interest, as the study was funded by Biosintética-Ache.

Sources of Funding

This study was funded by Biosintética-Aché.

Study Association

This study is not associated with any post-graduation program.

References

1. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The antihypertensive and lipid - lowering treatment to prevent heart attack trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker versus diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288: 2981-97.
2. Poulter N, Wedel H, Dahlöf B, Sever P, Beevers D, Caulfield M, et al. ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005; 366: 895-906.
3. Angeli F, Verdecchia P, Reboldi G, Gattobigio R, Bentivoglio M, Staessen J, et. al. Calcium channel blockade to prevent stroke in hypertension: a meta-analysis of 13 studies with 103,793 subjects. Am J Hypertens. 2004; 17: 817-22.
4. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double-blind studies. JAMA. 1996; 275: 1507-13.
5. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE, et al for the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival And Ventricular Enlargement trial. N Engl J Med. 1992; 327: 669-77.
6. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation Study [published correction appears in N Engl J Med. 2000;342:1376]. N Engl J Med. 2000; 342: 145-53.
7. Fox KM. European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003; 362: 782-8.
8. Rosendorff C. Calcium antagonists in the treatment of hypertension in patients with ischaemic heart disease. Expert Opin Pharmacother. 2003; 4: 1535-41.
9. Mason RP. Mechanisms of plaque stabilization for the dihydropyridine calcium channel blocker amlodipine: review of the evidence. Atherosclerosis. 2002; 165: 191-9.
10. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. Ann Intern Med.1992; 117: 234-42.
11. Weir MR. Incidence of pedal edema formation with dihydropyridine calcium channel blockers: issues and practical significance. J Clin Hypertens. (Greenwich) 2003; 5: 330-5.
12. Sica DA. Calcium channel blocker-related peripheral edema: can it be resolved? J Clin Hypertens. (Greenwich) 2003; 5: 291-4,297.
13. Harvey RM, Doyle EF, Ellis K,Farber SJ, Ferrer MI, Fischel EE, et al. Major changes made by the criteria committee New York heart association. Circulation. 1974; 49: 390.
14. Campeau L. Grading of angina pectoris [letter]. Circulation. 1976; 54: 522-3.
15. Sociedade Brasileira de Cardiologia. V Diretrizes brasileiras de hipertensão arterial. Arq Bras Cardiol. 2007;89: e24-e79.
16. Neal B, MacMahon S, Chapman N. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. Lancet. 2000; 356: 1955-64.
17. van Bemmel T, Gussekloo J, Westendorp RGJ, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. J Hypertens. 2006; 24: 287-92.
18. Bulpitt CJ, Beckett NS, Cooke J, Dumitrascu DL, Gil-Extremera B, Nachev C, et al, on behalf of the Hypertension in the Very Elderly Trial (HYVET) Working Group: results of the pilot study for the Hypertension in the Very Elderly Trial. J Hypertens. 2003; 21: 2409-17.
19. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective Studies Collaboration: age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360: 1903-13.
20. Sociedade Brasileira de Cardiologia. Diretrizes de doença coronariana crônica angina estável. Arq Bras Cardiol. 2004; 83(supl 2): 1-40.
21. Fox K, Garcia MA, Ardissino D, Buzman P, Camici PG, Crea F, et al. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology.Eur Heart J. 2006; 27: 1341-81.
22. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, et. al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized

controlled trial. JAMA. 2004; 292: 2217-26.

23. Sipahi I, Tuzcu EM, Schoenhagen P, Wolski KE, Nicholls SJ, Balog C, et. al. Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. J Am Coll Cardiol. 2006; 48: 833-8.

24. Julius S, Kjeldsen S, Weber M, Brunner H, Ekman S, Hansson L, et. al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. Lancet. 2004; 363: 2022-31.

25. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomized trials. BMJ. 2003; 326: 1427-31.