

# ANTIHYPERTENSIVE TREATMENT AND ITS IMPLICATIONS ON LIPOPROTEIN METABOLISM Of Patients in Care by a Hypertension and Diabetes Program in Brazil

René D. MARTINS, Renata de Sousa ALVES, Grazielle G. SILVA, Natália MARTINS, Silvânia VASCONCELOS, Ana ASSREUY, Alice MARTINS, Maria GORETTI QUEIROZ

## SUMMARY

Multiple risk factors for cardiovascular disorders, particularly hypercholesterolemia, are often present in hypertensive patients. Several studies have shown that antihypertensive drugs affect the lipid profile, increasing the risk of cardiovascular diseases. Here, it was investigated the lipoprotein metabolism alterations in a group of hypertensive patients in care by the Hypertension and Diabetes Program of a public hospital in Fortaleza-CE/Brazil. In this study, one hundred sixty nine serum samples from hypertensive patients (32-87 years old) under antihypertensive therapy were analyzed. Triglycerides, total cholesterol, cholesterol from high density lipoprotein (HDL) and from low density lipoprotein (LDL) serum levels were determined by enzymatic colorimetric method and AI and B apolipoproteins by immunoturbidimetric assay. The population enrolled was predominantly women (73.13%) and from these, 33.53% taking the monotherapy regimen, used angiotensin converting enzyme inhibitors (ACE-I). However, in combined therapy (66.47%) the most used drugs were the diuretics, especially in prescriptions associated to ACE-I. It was also observed that patients taking diuretics in monotherapy regimen showed significant effects in their serum lipid concentrations of lipids, in contrast with individuals taking combined therapy, which had no expressive alterations in their lipid profile. These results suggest that the antihypertensive therapy must be associated to a lipid monitoring process.

## RESUMO

### TRATAMENTO ANTIHIPERTENSIVO E SUAS IMPLICAÇÕES NO METABOLISMO LIPOPROTÉICO

**De Doentes Acompanhados por um Programa de Hipertensão e Diabetes no Brasil**  
Muitos fatores de risco para doenças cardiovasculares, particularmente hipercolesterolemia, estão frequentemente presentes em pacientes hipertensos. Diversos estudos têm mostrado que drogas antihipertensivas afetam o perfil lipídico, aumentando o risco de doenças cardiovasculares. No presente trabalho, foram investigadas as alterações lipoproteicas em um grupo de pacientes hipertensos abrangidos por um programa de Hipertensão e Diabetes de um hospital público em Fortaleza-CE/Brasil. Neste estudo, 169 soros de pacientes hipertensos (32-87 anos de idade) foram analisados no âmbito da terapêutica antihipertensiva. Os níveis séricos de triglicérides, colesterol total, das lipoproteínas de alta densidade (HDL) e de baixa densidade (LDL) foram determinados por método enzimático calorimétrico, e as apolipoproteínas AI e B por ensaio imunoturbidimétrico. A população envolvida foi predominantemente feminina (73.13%), e dessas 33.53% faziam

R.D.M., R.S.A., G.G.S., A.M., M.G.Q.: Departamento de Análises Clínicas e Toxicológicas. Faculdade de Farmácia. Universidade Federal do Ceará. Brazil  
N.M., S.V.: Departamento de Fisiologia e Farmacologia. Faculdade de Medicina. Universidade Federal do Ceará. Brazil  
A.A.: Universidade Estadual do Ceará. Brazil

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uso de monoterapia com inibidor da enzima conversora de angiotensina (ACE-I). Entretanto, em terapia combinada (66.47%), a droga mais utilizada foi o diurético, especialmente quando associado ao ACE-I. Foi ainda observado que pacientes fazendo uso de diuréticos em regime monoterápico mostraram efeitos significativos nas suas concentrações de lipídios séricos, em oposição aos que faziam terapia combinada que não apresentaram alterações expressivas em seus perfis lipídicos. Esses resultados sugerem que a terapia antihipertensiva deve ser associada a processos de monitorização lipídico.

## INTRODUCTION

Hypertension is considered one of the most important causes of premature death all around the world<sup>1</sup>. This pathogenesis is being frequently associated with multiple metabolic disorders, especially hypercholesterolemia<sup>2</sup> and insulin resistance, as a consequence of the reduction in the sensibility to glucose, which has been implicated in the pathogenesis of essential hypertension<sup>3,4</sup>. Patients with concurrent hypertension and dyslipidemia are at high risk of cardiovascular disease<sup>5</sup> and recent evidences suggest a relationship between hypertension and dyslipidemia, characterized, in most circumstances, by low serum levels of the high density lipoprotein (HDL), and high levels of triglycerides and low density lipoprotein (LDL)<sup>6-8</sup>.

The investigation for apolipoproteins A-I and B has been considered a sensible and specific parameter in the identification of ischemic cardiopathy risks<sup>9</sup>. Several studies have suggested the presence of apolipoprotein B (apo B) in atherogenic particles, mainly LDL, very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and lipoprotein (a) [Lp(a)]. In the other hand, apolipoprotein AI (apo AI) is found in non atherogenic particles, similar to the HDL type<sup>10</sup>.

The principal aim of the antihypertensive therapy is the reduction in atherosclerosis complications. However, some studies have demonstrated that, even significantly lowering the blood pressure, the cardiovascular events are still considerably present<sup>11</sup>. Several classes of drugs are available for the hypertension treatment<sup>12</sup>, but some of them such as diuretics and  $\beta$ -receptors blockers, adversely affect the lipoprotein profile<sup>13,14</sup>. This effect seems to occur via insulin resistance, leading to dyslipidemia<sup>4,14</sup>. The metabolic alterations, however, are reversible after the treatment disruption<sup>4,15,16</sup>.

In this study, it was investigated the disturbances in the lipoprotein metabolism in hypertensive patients in care by the Hypertension and Diabetes Program of a public hospital in Fortaleza-CE/Brazil, under antihypertensive therapy.

## MATERIALS AND METHODS

The study was conducted with 169 patients, aging between 32 and 87 years old via application of a questionnaire, inquiring about: medicine, blood pressure, life style, body mass index (BMI) and familiar history. The individuals included had systolic pressure equal or superior to 140 mmHg and/or diastolic pressure equal or superior to 90 mmHg, taking or not antihypertensive therapy. Patients were separated into two groups, according to the therapy regimen used. The monotherapy group included patients using a single antihypertensive drug, and the combined therapy group was composed by patients taking two or more antihypertensive agents for at least three months. Evaluating the influence of diuretics and beta-blockers in the lipid metabolism, patients taking ACE-I in a monotherapy regimen were used as control, since it is known that these antihypertensive agents do not affect the lipid profile<sup>13, 17</sup>. Lipoprotein and glucose levels were monitored by biochemistry analysis. Blood samples were collected after 12 hour of fastening for determining serum levels of glucose, triglycerides (TG), total cholesterol (TC) and the fractions HDL and LDL by enzymatic colorimetric methods (Labtest). The apolipoproteins AI and B were analyzed by immunoturbidimetric assay (Biotécnica) and dyslipidemias were classified into three groups hypertriglyceridemia, hypercholesterolemia or heterogeneous dyslipidemia, according to the border values for triglycerides (150 mg/dL) and total cholesterol (200 mg/dL).

Patients in treatment with the following medicine: lipid lowering, retinoic acid derivatives, tamoxifen, androgens, estrogens, fish oil or cyclosporine, and also with fasting serum glucose concentration > 126 mg/dL, or with hepatic and/or renal and thyroid dysfunctions, were excluded from the study.

The statistical analysis was done using the Epi info 6.04 program. For comparisons between means, Analysis of Variance (ANOVA), followed by Bonferroni, Student t test unpaired, Mann-Whitney or Kruskal Wallis were used when appropriated. Qui-square ( $\chi^2$ ) test and Fisher's exact

test were chosen for comparisons between proportions. Values were expressed as mean  $\pm$  SD and also in percentage. Median values were used for high amplitude data, as triglycerides measurements. Data were considered to be significant at  $p < 0.05$ .

## RESULTS

Table 1 – Distribution of risk factors by sex of hypertensive

Baseline characteristics	Female	Male	<i>p</i>
Percentage (%)	73.13	26.87	< 0.05
Age (Years)	57.29 $\pm$ 11.65	63.72 $\pm$ 9.13	< 0.05
<b>Blood Pressure (mmHg)</b>			
Systolic	144.59 $\pm$ 15.07	146.11 $\pm$ 14.39	> 0.05
Diastolic	90.61 $\pm$ 9.5	89.58 $\pm$ 11.11	
BMI (Kg/m <sup>2</sup> )	28.5 $\pm$ 4.08	29.01 $\pm$ 3.72	
Fasting glucose (mg/dL)	89.79 $\pm$ 11.86	90.29 $\pm$ 11.37	

BMI = body mass index

Table 1 shows the prevalence of women (72.6%) in the study and that the age of male individuals was proportionally significantly higher compared to the women studied. It was not observed significant differences in the diastolic or systolic pressures, neither in the fasting serum glucose concentration, nor in the body mass index (BMI) between male and female. However, all patients were overweighty.

Table 2 – Prescriptions of antihypertensive agents in mono- or combined therapy.

Drugs	(% <sup>a</sup> ) prescribed drugs <sup>#</sup>	Monotherapy (n=55)		Combined therapy (n=113)		<i>p</i>
		n	%	n	%	
Diuretics*	114 (67.5)	13	23.6	101	89.4*	< 0.05
ACE-I*	87 (51.5)	21	38.2	66	58.4*	< 0.05
Beta-blockers *	49 (29.0)	13	23.6	36	31.8	0.26
CCB**	21 (12.4)	3	5.5	18	15.9	0.12
CAA **	18 (10.7)	5	9.1	13	11.5	0.79

Statistic Tests = \*Qui-quadrado ( $\chi^2$  Thiazidic diuretics = 60.85;  $\chi^2$   $\beta$ -blockers = 1.26;  $\chi^2$  ACE-I = 7.19). \*\* Fisher's exact test. ACE-I – angiotensin converting enzyme inhibitors; CCB = calcium channel blockers; CAA = Centrally Acting Agents. # Number of prescriptions of each antihypertensive agent at any therapeutic regimen.

The prevalence of drugs and the therapy regimen used in the study are shown in table 2, demonstrating that combined therapy was applied to 66.1 % of patients and monotherapy regimen in to 33.9 % of patients. Diuretics (67.5

%), ACE-I (51.5 %) and beta-blockers (29%) were the most prescribed drugs. It can be was also observed that in the combined therapy the diuretics were the most prescribed medicine, being 36 % of them associated to ACE-I, and in the monotherapy regimen ACE-I was the principal group of drug of choice. Additionally, the study focused that only 14.9 % of hypertensive patients presented controlled levels of blood pressure (inferior to 140/90 mmHg), and being its majority was due to the use of monotherapy regimen in comparison to the combined therapy (**Figure 1**).

The lipid profile analysis pointed to the combined dyslipidemias the prevalent disturbance. The positive high correlation between total cholesterol and LDL was observed in all groups ( $0.72 < r < 0.94$ ), mainly in the hypercholesterolemic individuals, while the higher serum levels of triglycerides, associated to low level of HDL, showed prevalence among the hypertriglyceridemic patients.

In the lipid profile analysis during monotherapy the three most prescribed therapeutic agents were studied: thiazide diuretics,  $\beta$ -blockers and ACE-I. Patients treated with diuretics, in the monotherapy regimen, presented significant alterations in the lipoprotein metabolism, including total cholesterol, triglycerides and LDL, and also in apolipoprotein B, compared to those taking ACE-I. The group of patients using beta-blockers did not show significant alterations in their lipid profile, compared to the control group (ACE-I) – **Figure 2**. Additionally, in this investigation it was not observed significant alterations in the serum concentrations of HDL and apolipoprotein AI at any group studied.

Furthermore, among patients using associated therapy, it was not noticed significant differences in the lipid or apolipoproteins AI and B metabolism, although these patients have shown important alterations in these parameters (**Figure 3**).

## DISCUSSION

The prevalence of female patients in the population studied is in accordance to the results obtained by Lunet and Barros<sup>18</sup>, which highlights the women's interest for searching the health service. The low prevalence of some risk factors such as stroke, cerebral vascular accident and diabetes, seems to occur due to the search of individuals with these

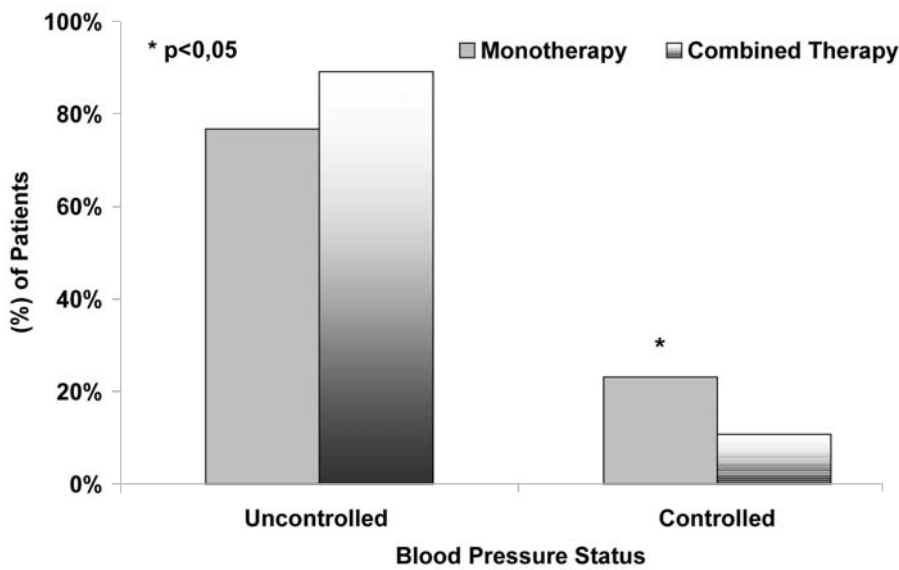


Fig 1 – Blood pressure control in mono- or combined therapy. Statistic Test = Qui-quadrado

complications for secondary attention centers by individuals with these complications.

The high positive correlation between total cholesterol and LDL, observed in different types of dyslipidemia, may be responsible for the intensification in the development of cardiac atherosclerosis diseases. Several lines of evidence, like animal studies, prospective epidemiologic studies, genetic forms of hypercholesterolemia, and controlled clinical trials, indicate that LDL is the major atherogenic lipoprotein<sup>19</sup>.

notherapy, observed in this study, follows the recommendation of the VII Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<sup>22</sup>. However, other studies have promised the use of monotherapy<sup>16, 23, 24</sup>.

Furthermore, diuretics showed to be the most prescribed drug in this study, similar to other investigations<sup>25</sup>, although some studies shows the prevalence of ACE-I<sup>23,24</sup>. These opposing results could be due to differences in the

Contrary, the serum levels of HDL and triglycerides seem to show an inverse correlation. This involves an increased expression of the cholesterol ester transference protein (CETP), and deficiency in hepatic lipases and apolipoprotein AI<sup>20</sup>. The HDL serum levels and the increased risk of CAD shows strong negative correlation, while the correlation between triglycerides and CAD is highly positive<sup>21</sup>.

The preference in the choice of the combined therapy in comparison to the mo-

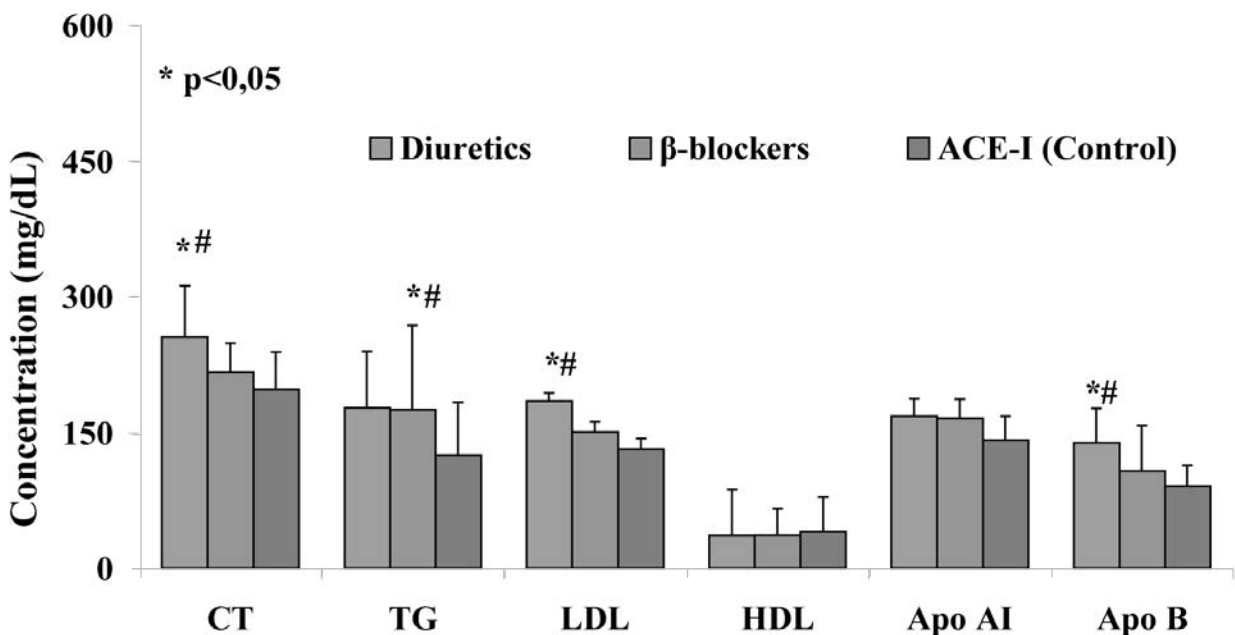


Fig. 2 – Lipid and apolipoproteins A1 and B profile in hypertensive patients taking monotherapy. Mean ± SD. Statistic tests= Student t test and Kruskal Wallis. # Diuretics versus ACE-I – Statistic F (1.24): CT=4.4; TG= 4.94; LDL= 5.27; apoB= 8.84. ACE-I = angiotensin converting enzyme inhibitors; CT = total cholesterol, TG = tryglicerides, LDL = low-density lipoprotein cholesterol; HDL= high-density lipoprotein cholesterol; Apo AI = apolipoprotein AI, Apo B= apolipoprotein B.

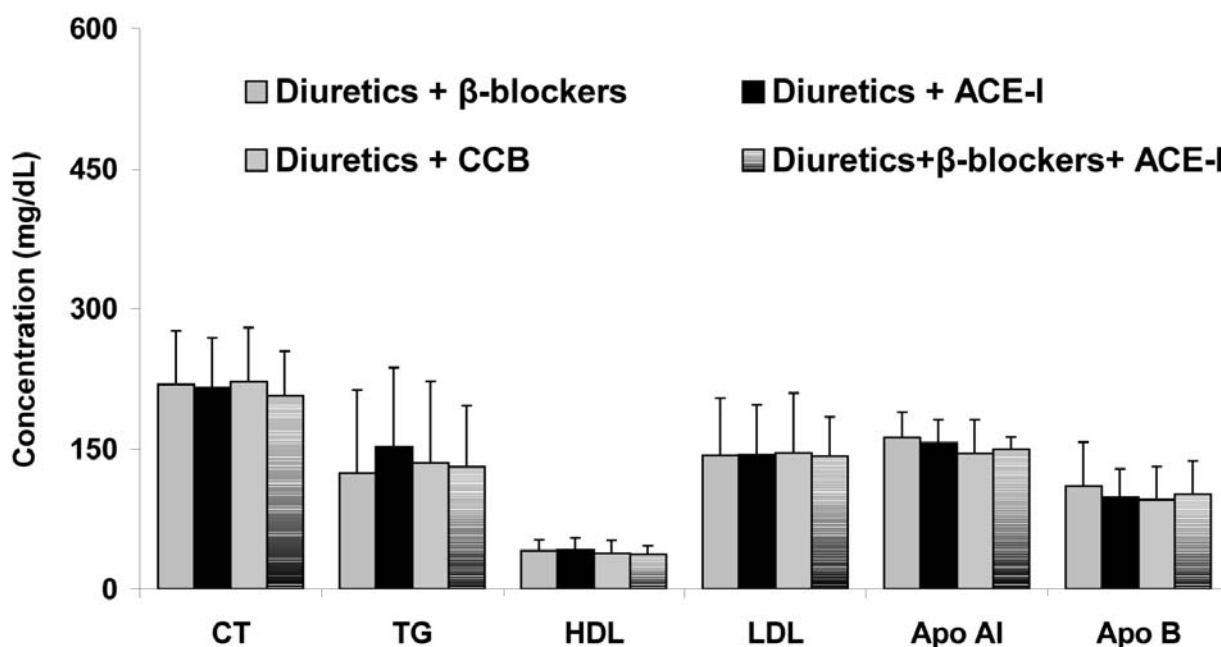


Fig. 3 – Lipid and apolipoproteins AI and B profile in hypertensive patients taking combined therapy. Mean  $\pm$  SD. Statistic Tests = ANOVA and Wilcoxon. ACE-I – angiotensin converting enzyme inhibitors; CCB= calcium channel blockers; TC = total cholesterol, TG= tryglicerides, LDL = low-density lipoprotein cholesterol; HDL= high-density lipoprotein cholesterol; Apo AI = apolipoprotein AI, Apo B= apolipoprotein B.

therapeutic regimens applied, since in our study the combined therapy was the regimen of choice.

Amongst the drugs used in the monotherapy regimen, the most prescribed drug was the ACE-I, which shows good tolerance by patients as the initial treatment of hypertension. In line with this, Esposti et al<sup>26</sup> observed that some Italian primary care centers prescribe mostly ACE-I as the initial antihypertensive treatment, especially for diabetics patients.

Hypertension remains uncontrolled in the majority of affected patients despite treatment<sup>27</sup>. Comparing the two groups of patients taking monotherapy or combined therapy, only 23.2% of the former and 10.81% of the latter, presented controlled blood pressure, showing an insufficient response to treatment. This inadequate hypertension control probably had occurred by the low buying power of the population studied. This makes difficult the adoption of a modified lifestyle by the population analyzed, which could reduce their clinical response to the antihypertensive treatment. In the United States, only 24% of hypertensive adults from 18 to 74 years old of age have their hypertension adequately controlled, and among patients being treated, only 55% achieve adequate blood pressure control<sup>28</sup>. Additionally, the incidence of controlled hypertension is lower in men than women and those aged above 75 years<sup>29,30</sup>.

The effect of thiazide diuretics and  $\beta$ -blockers agents upon the elevation of serum lipids has been intensively discussed<sup>4,17,31</sup>, and the diminished sensibility to insulin is considered to be the mechanism responsible for the worsen of dyslipidemia<sup>4</sup>. However, the validation of the use of  $\beta$ -blockers and diuretics in the hypertension treatment has been corroborated both by important American and European clinical trials<sup>32</sup>, reducing with efficacy the morbidity and mortality caused by cardiovascular disorders<sup>28,33</sup>.

The described lipid alterations observed in hypertensive individuals under treatment with diuretics may be one important factor responsible by its choice in combined therapy, since the adverse effects in the lipid metabolism occur mainly in patients taking elevated doses of these drugs<sup>4,15,16</sup>. In relation to the use of  $\beta$ -blocker agents, not only in association to other antihypertensive drugs, but especially the preference for selective  $\beta_1$  seems to play important role in the reduction of the side effects related to the lipid profile promoted by these agents<sup>32</sup>.

The antihypertensive treatment with  $\beta$ -blockers or diuretics is recognized to reduce mortality caused by cardiovascular disorders. Those differences can be explained by the impact degree caused by the presence of concomitant cardiovascular risk factors, such as dyslipidemia, glucose intolerance, diabetes or cerebrovascular accident, which contributes to the reduction in the effectiveness of the blood pressure control and in the therapeutic optimization<sup>4,34</sup>.

## CONCLUSION

The mechanisms involved in the antihypertensive effects upon protein metabolism and how they influence clinical responses still need more investigation. In fact, the evaluation of cardiovascular risks in hypertensive patients must involve serum lipid monitoring, especially when these individuals are under antihypertensive therapy with thiazide diuretics in order to ameliorate the clinical response and prevent additional risks of atherosclerosis disorders.

### Conflito de interesses:

Os autores declaram não ter nenhum conflito de interesses relativamente ao presente artigo.

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*Universidade Federal do Ceará, Brasil*