

Regression of carotid intima-media thickness with nifedipine in hypertensive patients

Regresión del grosor de la interfase íntima-media carotídea con nifedipina en pacientes hipertensos (REINA)

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Key words:

Systemic arterial hypertension, nifedipine, hydrochlorothiazide, carotid intima-media interphase, subclinical atherosclerosis.

Palabras clave:

Hipertensión arterial sistémica, nifedipina, hidroclorotiazida, capa íntima-media de la carótida, aterosclerosis subclínica.

ABSTRACT

Background: Calcium channel blockers (CCBs) have proved to reduce both blood pressure levels and cardiovascular outcomes, including the development of atherosclerosis. The INSIGHT study showed a less pronounced progression of carotid intima-media thickness (IMT) in patients treated with nifedipine (NIF) vs. those treated with diuretics, but because IMT was normal in both groups, it was difficult to assess the anti-atherosclerotic effect of NIF. We compared the effect of NIF or hydrochlorothiazide (HCTZ) on atherosclerosis regression in hypertensive patients with abnormally thick IMT. **Patients and methods:** 37 hypertensive patients were randomly assigned to be treated with slow release-NIF (30 mg) and 46 to HCTZ (25 mg), all of them with IMT > 0.6 mm. IMT, lipid profile, and serum uric acid, potassium, and glucose were analyzed at baseline and 12 months later. **Results:** Blood pressure was equally well controlled with both treatments. No biochemical abnormality was observed in neither groups. IMT was reduced 35% in the NIF group in comparison to 9.3% in HCTZ group. **Discussion:** BBCs restore endothelial function, exert antioxidant activity and limit smooth muscle cells growth and proliferation, thus inhibiting fundamental atherogenic phenomena. Our results show a clear regression of IMT, marker of subclinical atherosclerosis with NIF. **Conclusion:** Both treatments were equally effective reducing blood pressure. HCTZ did not cause metabolic disarrays, but only NIF induced IMT regression. Basal IMT is a main determinant of regression.

RESUMEN

Antecedentes: Los bloqueadores de los canales de calcio (BCC) han demostrado reducir tanto los niveles de presión arterial como los eventos cardiovasculares, incluyendo el desarrollo de la aterosclerosis. El estudio INSIGHT mostró una progresión menos pronunciada del grosor de la capa íntima-media de la carótídea (GIMC) en pacientes tratados con nifedipina (NIF) vs. los tratados con diuréticos, pero debido a que el GIMC fue normal en ambos grupos, resultó difícil evaluar el efecto anti-aterosclerótico de la NIF. El presente estudio comparó el efecto de la NIF o hidroclorotiazida (HCTZ) en la regresión de aterosclerosis en pacientes hipertensos con GIMC anormalmente gruesa. **Pacientes y métodos:** 37 pacientes hipertensos fueron asignados al azar para ser tratados con NIF de liberación lenta (30 mg) y 46 a HCTZ (25 mg), todos ellos con GIMC > 0.6 mm. GIMC, perfil lipídico, y ácido úrico en suero, potasio y glucosa se analizaron al principio y 12 meses más tarde. **Discusión:** Los BCC restauran la función endotelial, ejercen actividad antioxidante y limitan el crecimiento y la proliferación de las células del músculo liso, inhibiendo así fenómenos aterogénicos fundamentales. Nuestros resultados muestran una clara regresión del GIMC, marcador de aterosclerosis subclínica, con NIF. **Conclusión:** Ambos tratamientos fueron igualmente efectivos para reducir la presión arterial. HCTZ no causó desorden metabólico, pero sólo la NIF induce la regresión del GIMC. El GIMC basal es un determinante principal de la regresión.

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BACKGROUND

The clinical, epidemiological and socioeconomic importance of systemic arterial hypertension (SAH) resides in its capacity to damage the entire arterial vascular tree, from

aorta to capillaries, through several intertwined pathogenic mechanisms, including abnormal hydraulic forces and their associated neuro-humoral derangements, nitroxidative stress, inflammation, and endothelial dysfunction. In that manner, SAH is involved in the genesis of

several forms of vascular disease such as atherosclerosis, hypertensive arteriosclerosis and arteriolosclerosis, senescent arteriosclerosis, lipohyalinosis and fibrinoid necrosis. Furthermore, SAH is also implicated in the direct hypertrophic lesion of the left ventricular myocardium, base of hypertensive heart disease.¹⁻⁵ Undoubtedly, atherosclerotic plaques are the most threatening lesions caused by SAH, either alone or in association with other risk factors. Atherosclerotic vascular disease is preceded by a long free-symptoms period within which the finding of such asymptomatic lesions would allow the implementation of prophylactic interventions that could significantly delay clinical outcomes. In this context, high-resolution B-mode carotid ultrasonography is a reliable, repeatable, noninvasive, safe, and reasonably low-cost study, that is capable of detecting not only the existence of advanced atherosclerotic plaques, but also the abnormally augmented thickness of intima-media interphase (IMT), a condition that presents before the development of full-blown raised atheromatous lesions, thus somehow foretelling the occurrence of stroke or coronary syndromes.⁶

In the other hand, although all modern antihypertensive drugs are equally useful in attenuating high blood pressure, they differ in their potential to reduce vascular damage and splanchnic outcomes. Calcium channel blockers (CCBs) are useful therapeutic agents, with solid evidence about their antihypertensive power as well as cardiovascular protection.^{7,8} Even when some negative statements^{9,10} have been published in regards of calcium antagonists as antihypertensive drugs, several seminal large-scale studies have proven, beyond any doubt, their efficacy and safety, including an antiatherosclerotic effect.^{8,11,12} For example, the INSIGHT study¹³ compared the antihypertensive, metabolic, and antiatherosclerotic effects of two therapeutic regimes in high-risk hypertensive patients: slow-release nifedipine or a diuretic combination. The trial and one of the sub-analysis, the IMT-INSIGHT,¹⁴ showed a less pronounced progression of IMT, altogether with the same grade of blood pressure control and reduction of cardiovascular risk in the nifedipine-treated patients. The fact that basal values of IMT in both groups were within

normal ranges, overshadowed the clear-cut effect of nifedipine on subclinical atherosclerosis progression. Hence the purpose of this study was to compare the effects of nifedipine vs. hydrochlorothiazide on metabolic and blood pressure parameters as well as on IMT regression in hypertensive patients who presented with abnormally thickened carotid intima-media interphase at baseline.

PATIENTS AND METHODS

We conducted a randomized clinical trial with two parallel arms, one receiving slow-release calcium channel blocker (nifedipine) and the other a thiazide diuretic (hydrochlorothiazide). Hypertensive outpatients, of both genders, aged ≥ 20 years old, were recruited and randomly allocated in one of the two treatment groups. A convenience sample of 94 patients was assembled.

The study was approved by Institutional Ethics and Research Committees, and was conducted according with the Declaration of Helsinki, Good Clinical Practices and Mexican Federal Regulations.¹⁵⁻¹⁷ Patients were selected according to the following criteria: SAH grades 1 or 2 (Guidelines of the European Society of Cardiology/European Society of Hypertension),¹⁸ with systolic blood pressure (SBP) 140-179 mmHg, and diastolic blood pressure (DBP) 90-109 mmHg; IMT ≥ 0.6 mm; treatment-naïve or treated with β -blockers, ACE inhibitors or angiotensin receptor blockers. Patients were not included if they had grade 3 hypertension, diabetes mellitus, severe hypercholesterolemia, significant cardiovascular complications, severe systemic diseases (e.g., malignancies or HIV infection), history of drug or alcohol abuse. Women of child-bearing age, without a definite contraceptive method were also excluded.

In all patients, body weight was measured with a calibrated scale and recorded in kg; height was obtained in meters with a wall-stadiometer and body mass index (BMI) was further calculated. Blood pressure was measured in the sitting position, twice, with mercurial sphygmomanometers, following the standardized technique.¹⁸ Metabolic screening was performed by means of colorimetric assay kits -according with the manufacturer's instruc-

tions- and included fasting serum glucose, creatinine, uric acid, total cholesterol (TC), high-density lipoproteins cholesterol (HDL-c), and triglycerides (TG). Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald formula.¹⁹

IMT measurements were obtained using a high-resolution B-mode ultrasound machine (SONOS 7500) and a 7.5 MHz multi-frequency linear array probe, with the patient lying in supine decubitus, and the head, slightly hyperextended, rotated to the opposite side of examined carotid. Ultrasound examinations were performed by a single certified ultrasonographer, blinded to the type of treatment. B-mode images of the right carotid artery were obtained and IMT was measured by manual technique using electronic calipers, similar to the method described by Sidhu and Desai.²⁰ For the purpose of this study, four points were selected for IMT measurements: the far and near the wall of the common carotid artery, one cm bellow the bifurcation (points 1 and 2),

and the far and the near wall of the common carotid artery at the bifurcation level (points 3 and 4). The average IMT of these four points was considered in the final analysis.

All antihypertensive medication was suspended for a wash-out period of two weeks. Patients were then randomly assigned to receive, at the beginning, either 30 mg of slow-release nifedipine (NIF), or 25 mg of hydrochlorothiazide (HCTZ); however, if no SAH control was achieved, additional therapy of 100 mg of metoprolol, daily, was allowed. Patients were examined at the start of the running period, and then at three, six and twelve months later. The examination included blood pressure determination and the IMT measurement. Also, a blood sample was drawn to measure the aforementioned biochemical variables. If blood pressures goals (< 140/90 mmHg) were not attained, medication doses could be titrated up to 60 mg of nifedipine or 50 mg de hydrochlorothiazide. *Figure 1* summarizes the study's flow chart.

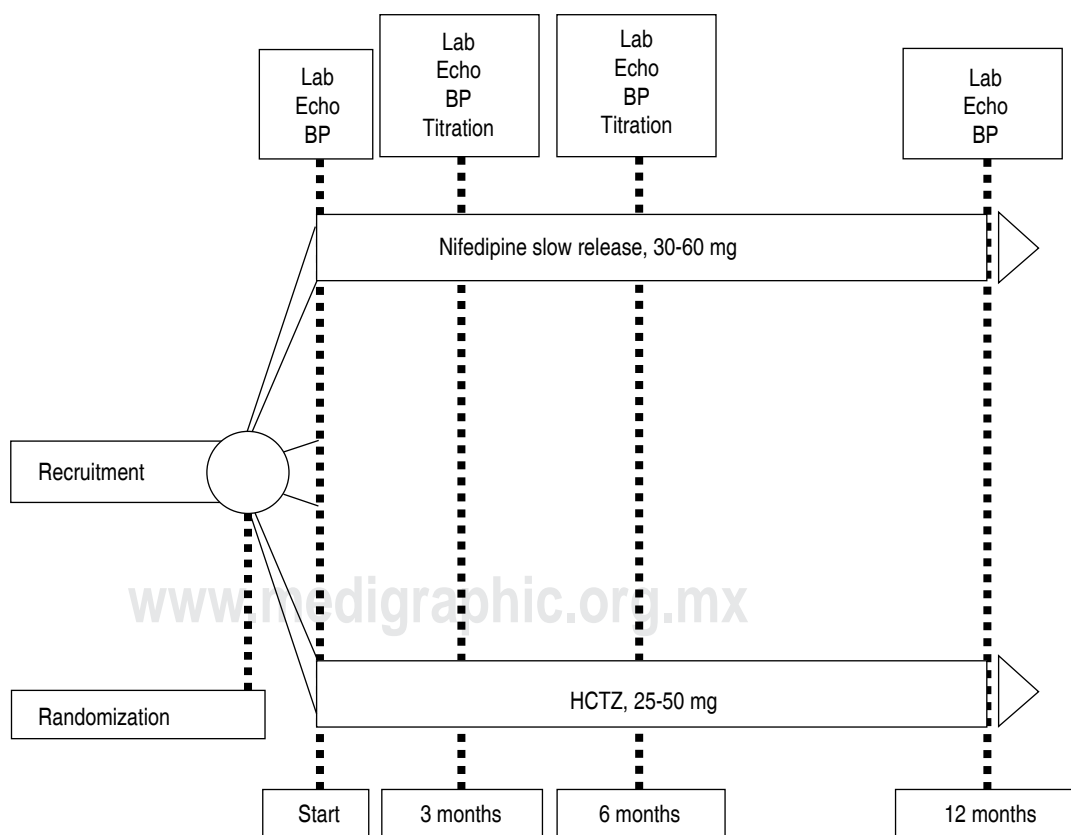


Figure 1.

Study's flow chart.

Lab: laboratory; Echo: IMT measurement by B-mode ultrasonography; BP: blood pressure measurement; HCTZ: hydrochlorothiazide.

Statistical analysis. The software package used in the present study was SPSS v.16.0. Quantitative variables are presented as mean \pm standard deviation; qualitative variables are presented as frequencies (percentages). Intragroup differences were assessed using repeated-measurements ANOVAs followed by Tukey's *post hoc* tests; whilst independent t-tests were performed in order to assess intergroup differences. Furthermore, we conducted bivariate and multivariate regression analysis. All tests were considered as statistically significant when $p < 0.05$.

RESULTS

83 (37 NIF and 46 HCTZ) patients completed the trial hence a *per protocol* statistical analysis was performed. The main causes of withdrawal were consent retirement, lack of compliance or change of address.

Table I. Anthropometric and demographic baseline data.

Variable	NIF n = 37	HCTZ n = 46	p
Age, years	56 \pm 11	57 \pm 10	n.s.
Proportion of women, %	72	78	n.s.
Height, m	1.55 \pm 7	1.56 \pm 7	n.s.
Weight, kg	81 \pm 16	74 \pm 14	n.s.
BMI, kg/m ²	33.5 \pm 6.7	30.5 \pm 6.4	n.s.

Initials as in the text. Data are presented as mean \pm standard deviation.

Anthropometric and demographic basal data were similar in both groups (Table I). It is worth mentioning that overweight and obesity presented as the prevalent nutritional phenotype, considering both means and standard deviations. In terms of gender, the proportion of women was greater in both groups.

Both treatments significantly reduced blood pressure levels in the vast majority of patients (Table II). It was noticeable that such reduction occurred since the first trimester, but the maximal descent was seen at the end of the study.

Neither metabolic nor anthropometric variables showed significant differences, in both, intragroup or intergroup analysis (Table III). Regarding adverse effects, only 5 cases of moderate ankle edema were observed in the nifedipine-treated patients, against nil in the diuretic treated group.

Finally, as seen in figure 2, mean carotid IMT was similarly abnormal at baseline: 0.85 mm in NIF group and 0.86 in the HCTZ group. However, while IMT descended scarcely and not significantly ($\approx 9\%$ by the end of the study) in HCTZ-treated patients, strikingly, in NIF-treated patients, such descent was $\approx 35\%$ (from 0.85 to 0.55 mm, $p < 0.05$). Table IV shows the coefficient values comparing IMT reduction and other variables; the only significant correlation ($p < 0.05$, $r = 0.66$) was, precisely, the type of treatment (i.e., either NIF or HCTZ).

DISCUSSION

It has been established that the main goal in the treatment of SAH is the reduction and/

Table II. Blood pressures through the study.

Groups	Basal		3 months		6 months		12 months	
	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg
NIF	140 \pm 23	88 \pm 8	130 \pm 15*	79 \pm 9*	129 \pm 9*	79 \pm 5*	126 \pm 34*	77 \pm 4*
HCTZ	143 \pm 8	88 \pm 8	133 \pm 8*	82 \pm 2*	136 \pm 4*	81 \pm 5*	128 \pm 12*	75 \pm 7*
p	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Initials as in the text. Data are presented as mean \pm standard deviation. * $p < 0.05$ after repeated measurements ANOVA and Tukey's *post hoc* tests (vs. own baseline); p = ns after Student's independent t-test.

Table III. Biochemical and anthropometric variables.

Variables	Groups	Basal	12 months	p
Glucose, mg/dL	NIF	92.9 ± 16	93.6 ± 12.9	n.s.
	HCTZ	94.3 ± 11.9	94.3 ± 16.6	
Uric acid, mg/dL	NIF	5.1 ± 1	5.4 ± 1.4	n.s.
	HCTZ	5.2 ± 1.35	6 ± 1.4	
Potassium, mEq/L	NIF	4.2 ± 0.5	4.2 ± 0.5	n.s.
	HCTZ	4.13 ± 0.37	3.9 ± 0.41	
Creatinine	NIF	0.86 ± 0.20	1.36 ± 0.22	n.s.
	HCTZ	0.82 ± 0.33	0.92 ± 0.24	
TC, mg/dL	NIF	204.1 ± 41.6	201.6 ± 45.5	n.s.
	HCTZ	206 ± 50	208.6 ± 43.9	
HDL-c, mg/dL	NIF	52.1 ± 13.4	53.5 ± 15.8	n.s.
	HCTZ	52.4 ± 11.6	50.8 ± 9.8	
TG, mg/dL	NIF	155.3 ± 66.7	152.4 ± 86.5	n.s.
	HCTZ	150 ± 93.5	186.9 ± 116.2	
LDL-c, mg/dL	NIF	116.4 ± 30.7	117.6 ± 38.1	n.s.
	HCTZ	105.3 ± 38.5	128.2 ± 40.8	
Weight, kg	NIF	81 ± 16	79 ± 15	n.s.
	HCTZ	74 ± 14	74 ± 13	
BMI, kg/m ²	NIF	33.5 ± 6.7	33.1 ± 6.2	n.s.
	HCTZ	30.5 ± 6.4	30.5 ± 5.8	

Initials as in the text. p = ns after both Student's independent and paired t-tests.

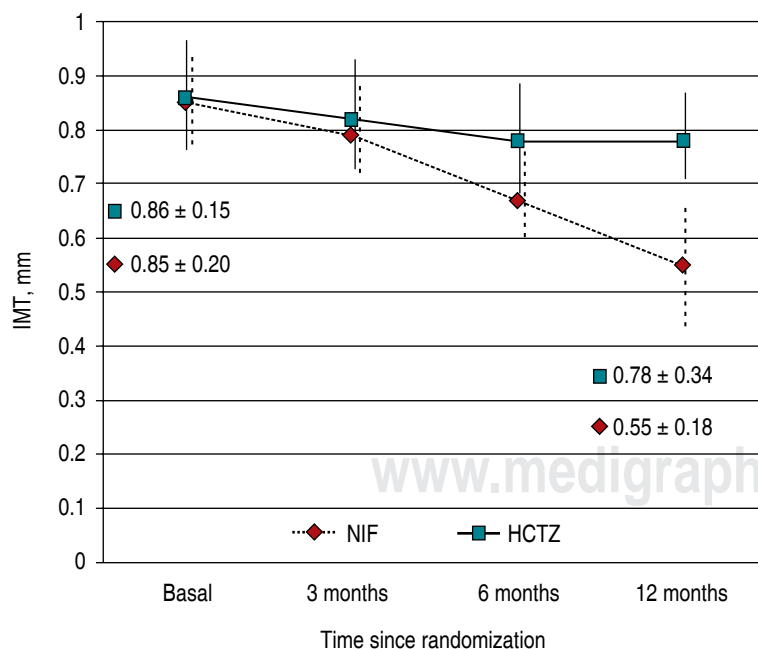


Figure 2. Intima-media thickness in both treatment groups.

or delay of vascular and organ damages.¹⁸⁻²⁴ Although all modern antihypertensive drugs have been proven to lower both, high blood pressure and overall cardiovascular risk, there are pronounced differences -among antihypertensive drug families- regarding specific vascular and end-organ damage protection, e.g., regression of left ventricular and arterial hypertrophy, renal safeguard, antidiabetic effects, and antiatherosclerotic or antischemic effects, amidst others. As coronary and cerebral atherosclerotic lesions are common cause of death and disability in modern societies, the main purpose of antihypertensive treatment must be the reduction of atherosclerotic complications in those essential target organs. Very unfortunately, atherosclerosis is clinically silent during a long period of time, hence its first clinical manifestation is often a devastating or lethal coronary or cerebrovascular event.^{25,26} In this sense, ultrasonographic IMT measurement is a relatively cheap and reliable method

Table IV. Correlation among IMT reduction and other variables in bivariate and multivariate analysis.

Variable	Correlation coefficient	Bivariate analysis	Multivariate analysis
	r	p	p
Type of treatment	0.66	0.001	0.02
Age	0.12	0.84	0.55
Gender	0.06	0.63	0.10
Height	0.20	0.70	0.09
Weight	0.15	0.68	0.55
BMI	0.12	0.45	0.60
Blood pressure	0.24	0.57	0.62
HDL-c	0.18	0.41	0.69
LDL-c	0.10	0.60	0.25
TG	0.12	0.70	0.38

Initials as in the text.

to determine early atherosclerotic changes, thus allowing the implementation of pharmacologic and lifestyle interventions aimed to slow down or even induce regression of the atherosclerotic process. Nevertheless, data from multiple studies have pointed out that although IMT has an acceptable correlation with future cardiovascular outcomes and the extent of coronary atherosclerosis,^{27,28} it is not superior to the traditional stratification of risk factors for cardiovascular risk.²⁹

Carotid IMT is reduced by several therapeutic interventions, among them, the use of antihypertensive drugs.³⁰ In several studies, CCBs have been proven to effectively reduce the progression of carotid IMT,³¹ and in fact, much better than diuretics, β -blockers or ACE inhibitors.^{30,32} The IMT-INSIGHT substudy,¹⁴ showed that while a combination of two diuretics, hydrochlorothiazide and amiloride, did not influence carotid thickening, a slow-release form of nifedipine retarded the atherosclerotic progression. Nevertheless, baseline values of IMT, in both groups, were within the limits of normality, so the clear-cut antiatherosclerotic effect of both treatments was only revealed by a rather complicated analysis in which histograms

of individual slopes of IMT modifications during a period of four years were plotted in order to visualize small differences in the thick of carotid wall. The yielding results were that the diuretic combination did not change the progression of IMT, while nifedipine caused a somehow negative slope, indicating a scanty regression of wall thickening. It was also noticed, that this lower slope correlated with increased baseline IMT. Of course, it is illusory to expect a great reduction of carotid IMT if there is no thickening at all at the base. This methodological flaw explained, for example, the «failure» of the combination of simvastatin/ezetimibe in diminishing the carotid IMT in patients with familial hypercholesterolemia (ENHANCE study),³³ but no subclinical atherosclerosis. As one of the ENHANCE study stated:³⁴ the «most important determinant of any clinical trial... is to have the presence of disease at baseline». In contrast, the present study included only patients with abnormally gross carotid IMT, i.e., with «disease at baseline». It was certainly surprising that the NIF-treated patients showed such significant IMT reductions, far out of the common results found in other trials. There is a possible explanation, raised by Orio's findings of an IMT reduction $\approx 20\%$ in women with polycystic ovary syndrome treated with metformin:³⁵ the anti-inflammatory effect of certain drugs (e.g., statins, metformin, pioglitazone, CCBs) can shrink -in a short time- the carotid wall due to the attenuation the inflammatory process that accompanies all vascular risk factors. These antinflammatory changes that result in diminishing wall volume and thickness, are significantly more rapid than the slower process of true atherosclerotic regression. Of course, this is just a speculative consideration that is not sustained with the data of this study.

Yet another hypothesis for elucidating the herein found results is the fact that there are substantial pleiotropic effects of CCBs beyond their remarkable antihypertensive effects. As it is well known, the starting point of vascular damage, cause by all vascular risk factors is a triad composed by endothelial dysfunction, nitroxidation and inflammation.³⁶ Dihydropyridine or nifedipine-like CCBs (DHP-type CCBs), block the membrane L-type calcium channel thus decrease intracellular calcium. This increase of intracellular calcium activates

endothelial nitric oxide (NO) synthase (eNOS) enhancing NO availability. Moreover, some CCBs, like nifedipine, have notorious effects as superoxide scavengers. Since a practical (although excessively simple) definition of endothelial dysfunction is a reduced NO availability and an augmented production of reactive oxygen substances, CCBs can restore the equilibrium between these two dialectic antagonists. Furthermore, there are evidences that DHP-type CCBs exert antioxidant effects limiting the oxidation of LDL cholesterol, fundamental phenomenon in atherogenesis. In the same manner, vascular smooth muscle cells (VSMC) growth and proliferation is another complex and multifactorial event in atherogenesis, in which calcium is directly involved.³⁷ So, the reduction of intracellular calcium inhibits the development of both, the primary *atherosis*, and the later phenomenon, *sclerosis*, that in sequence yield to the growth of atherosclerosis plaques. The bivariate and multivariate analysis in our study showed that the only responsible of the IMT reduction was the type of treatment.

Otherwise, both treatments were equally effective in attaining therapeutic goals. In the patients of this study, no were observed the frightful metabolic disarrays attributed to diuretics. In fact, at the end, serum potassium was lower, and uric acid was higher in the diuretic-treated group, but the statistical differences were not significant.

CONCLUSION

Our data show that both treatments (CCBs and HCTZ) are equally effective as antihypertensive regimes. Also, they show that in these patients, the metabolic effects of thiazides were unimportant. The reduction of carotid IMT, observed by a blind to treatment researcher, is in accordance with other observation around the world. Our results emphasizes that the basal magnitude if IMT is a main determinant of its pharmacological regression. We admit the limitations of the study: the essay was not double blind; the lack of two different sonographers, the relative small size of the sample and the semi-automatized measuring of wall borders.

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