

# Changes in Lipid and Lipoprotein Values during a Cross-Over Treatment of Doxazosin, Moduretic and Amlodipine in Hypertensive Patients

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## Abstract

A cross-over study, comparing the effects of doxazosin, moduretic and amlodipine on plasma lipid and lipoprotein levels in 9 hypertensive Nigerians aged 35 to 65 years is presented. Doxazosin therapy had favourable lipid changes characterized by a statistically significant reduction in total cholesterol (TC) at 6 months. Though consistent reduction was observed in total triglycerides (TG) low density lipoprotein cholesterol (LDL-C), very low density lipoprotein-cholesterol (VLDLC) up to 6 months, no effect was seen on high density lipoprotein cholesterol (HDLC). This is against unfavourable increments in the mean values of TC, VLDLC, LDLC/HDLC and decrease in HDLC/TC during moduretic treatment phase. Amlodipine therapy did not alter the lipid and lipoprotein levels. The non-significant variation in the mean high density lipoprotein-cholesterol (HDLC) level observed with these agents, seem to suggest that HDL-cholesterol metabolism may be maintained during antihypertensive pharmacotherapy (JPMA 44:166, 1994).

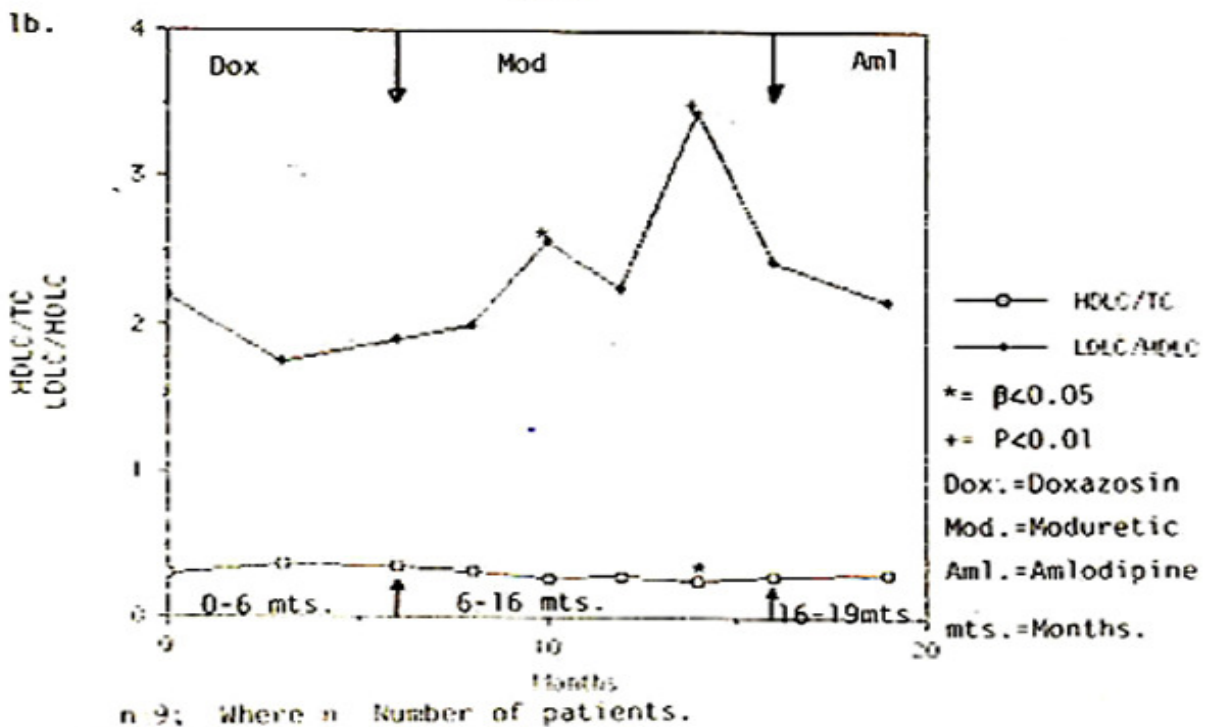
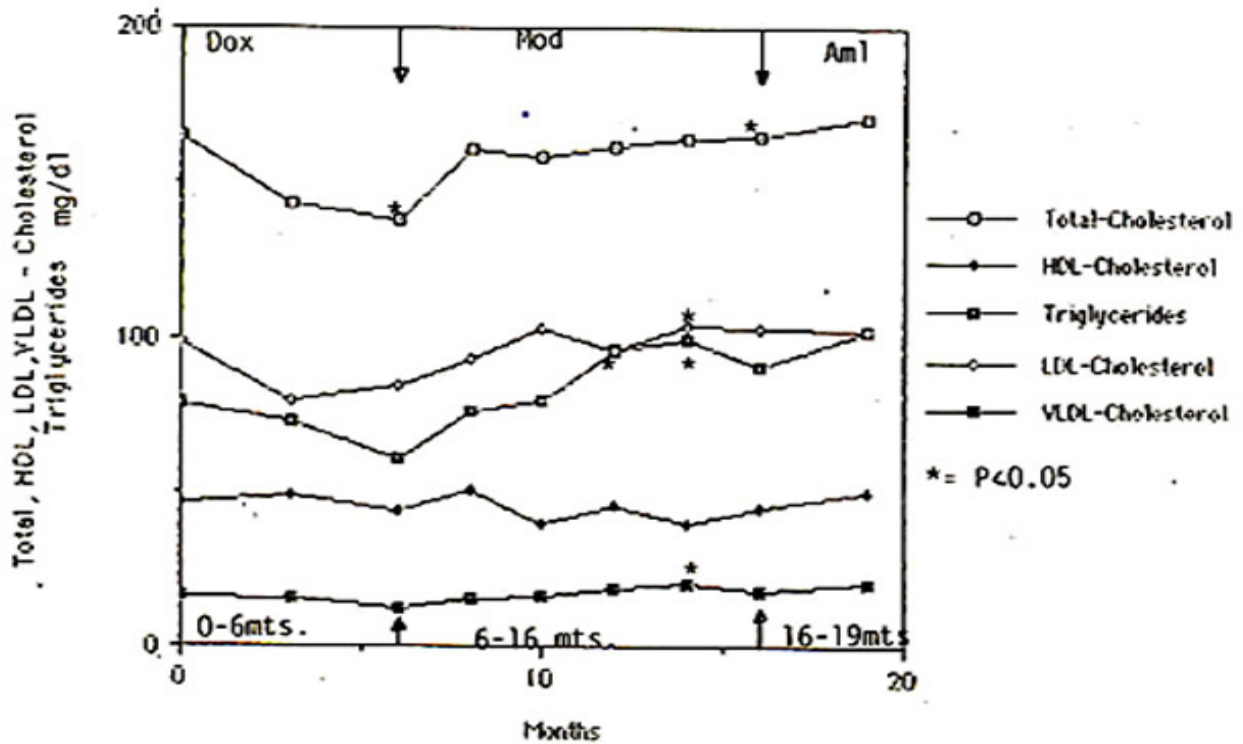
## Introduction

Doxazosin - an alpha selective inhibitor and amlodipine - a calcium channel blocker were recently introduced into treatment of hypertension. The third drug moduretic is a diuretic and consist of hydrochlorothiazide and amiloride hydrochloride and its use in the treatment of hypertension has long been recognised. In a comparative study of doxazosin and atenolol<sup>1,2</sup>. doxazosin was found to lower triglyceride, while the levels of HDL-cholesterol, HDLC/TC increased and atenolol showed the opposite. Both doxazosin and atenolol did not have any effects on total cholesterol concentration<sup>2</sup>. A similar comparison between the lipid changes during doxazosin and nitrendipine treatment did not reveal any significant variations between the two treatment groups<sup>3</sup>. Lipid and lipoprotein levels studied during the addition of doxazosin to the treatment regimen of patients not responsive to nifedipine showed that total cholesterol, triglyceride, HDLC and HDLC/TC did not statistically differ from its baseline value after the combined anti-hypertensive treatment<sup>4</sup>. Since the hallmark of anti-hypertensive pharmacotherapy depends on the ability of the drugs to exhibit maximal therapeutic efficacy with minimal side effects; we, therefore, evaluated the lipid and lipoprotein changes in the same hypertensive patients treated with three different classes of anti-hypertensive agents in a double-blind cross-over fashion. This may help to confirm the side effect profiles of these anti-hypertensive agents in our patients.

## Patients and Methods

Initially thirty patients aged 35 to 65 years with essential hypertension were selected for this study from the hypertension clinic of the University College Hospital, Ibadan, Nigeria. As a result of non-response and/or non-compliance nine patients were able to complete the 19 months study period. The patients were all Nigerians and the diagnosis of essential hypertension was established in accordance with World Health Organisation criteria, with moderate to severe elevation of blood pressure. Some of the patients who had been previously treated with antihypertensive drugs had their drugs withdrawn for a washout period of 2 weeks. The patients were not on any dietary regulation or other form of treatment throughout the study period. This was a double-blind, crossover study, which consisted three phases of washout/baseline, titration and maintenance. The blood pressure (sitting and supine), pulse rate and weight at the end of the 2 weeks washout period were recorded as baseline values. An average of two diastolic blood pressure readings in the range of 105-130 mmHg in the sitting and supine positions at the end of the 2 weeks washout period was regarded as the cut-off point for the patients' inclusion in this study. Upon selection for the study, the patients were placed on doxazosin treatment and maintained on the dosage in which the patients showed response for a period of 6 months, by which time the blood pressures were reduced in the range of mild to moderate. At the end of 6 months doxazosin therapy, the patients were switched over to one to two tablets of moduretic daily (equivalent to 50 mg hydrochlorothiazide and 5 mg amloride hydrochloride) for a period of 10 months. After the ten months of moduretic therapy the blood pressure was controlled and the patients were switched over to amlodipine therapy for another 3 months. The patients were seen fortnightly at the clinic by the same physician for full clinical assessment throughout the study period and in each case blood pressure was recorded twice using a mercury sphygmomanometer (accuson(R)) Drugs were dispensed in the clinic by a co-investigator in amounts sufficient to last until the next visit to encourage compliance with the dosage schedule. At the beginning and after every three months (in the case of doxazosin and amlodipine therapies) and two months (in the case of moduretic therapy), 5 ml of venous blood was withdrawn from each patient following an overnight fast (10-12 hours) for lipid analysis. The blood was collected in a bottle containing dry sodium EDTA (1 mg/dl) placed on ice. Blood was centrifuged quickly after collection at 4°C and the plasma separated and stored at -20°C before analysis. High-density lipoprotein (HDL) was isolated from the other lipoproteins by the method of Burstein and Samaille<sup>6</sup>. The HDL and total cholesterol were determined by the modified method of Libermann-Burchard reaction as described by Searcy and Berquist<sup>7</sup>. Plasma triglyceride was estimated by the method of Gottfried and Rosenberg<sup>8</sup>, low density lipoprotein cholesterol (LDLC) and VLDL-cholesterol were calculated using the Friedwald formula<sup>9</sup>. For each assay, a commercial quality control (Well control I and II reagents) of known values were always included. The mean values of the lipid variables before and at every period of measurement were compared using the paired t-test.

## Results



**Figure 1a, 1b. Effect of plasma lipid and lipoprotein levels before and during a cross-over of doxazosin/moduretic/amlodipine treatments.**

As shown in figures 1a and b, the mean values of TC, TG, LDLC, VLDLC and ratio LDLC/HDLC consistently declined from the pre-treatment values during doxazosin treatment phase. The decrease in the mean value of TC at 6th month of doxazosin therapy was significant ( $P < 0.05$ ) when compared with the previous values at pre-treatment and 3rd month of therapy. These lipid and lipoprotein parameters

started to increase during the moduretic treatment phase (6-16 months) and the levels of increment were statistically significant ( $P < 0.05$ ) when compared with the values during doxazosin treatment phase. As the patients were switched from moduretic to amlodipine treatment, the levels of the lipid parameters stopped to rise, so that the mean values during amlodipine phase did not show any statistically significant variation when compared with the values of the previous measurement. Mean HDLC/TC ratio showed some insignificant elevations during doxazosin treatment phase, thereafter the ratio (HDLC/TC) started to fall during moduretic treatment phase and this was significant at the 14th month ( $P < 0.05$ ). The ratio did not show any further decrease after the patients were switched to amlodipine. The mean HDL- cholesterol values showed slight and insignificant variations during the three treatment phases.

## Discussion

To study the lipid changes, the cross-over study was designed to present a comparison and confirmatory picture of how our patients may react with the three different classes of anti-hypertensive agents. Doxazosin treatment phase had beneficial effects on lipid and lipoprotein levels (characterised by a decrease in TC level) in Nigerian patients. Our results revealed adverse lipid and lipoprotein changes (increases in TC, LDLC, TO, VLDLC, LDLCIHDL and decrease in HDLC/TC) during moduretic treatment phase. Non-significant variations in the lipid and lipoprotein parameters during amlodipine treatment phase confirm the inertness of amlodipine previously reported in the same population<sup>5</sup>. The observed insignificant changes in the HDL-cholesterol levels during the three treatment phases, may suggest that HDL-cholesterol metabolism may not be altered by anti-hypertensive agents in the Nigerian patients. Although our earlier reports showed significant reduction in HDL-cholesterol especially during the short-term moduretic therapy alone. There have not been similar three way cross-over studies with these drugs either in Nigeria or elsewhere; however, there have been reports of other cross-over studies involving at least two anti-hypertensive agents in different populations<sup>10,11</sup>. Of 13 white men, who completed the study, prazosin (but not doxazosin) was shown to lower plasma total cholesterol as against an increase in triglyceride and VLDLC values during propranolol therapy. The report by Stamler et al.<sup>11</sup> documented that eight patients who were assigned to prazosin monotherapy before crossing over to hydrochlorothiazide and another set of 13 patients who were treated with hydrochlorothiazide before crossing over to prazosin therapy, had their total cholesterol levels lowered by prazosin. They also observed no significant variations between the two drugs with respect to levels of high-density lipoprotein or its subfraction, or low-density lipoprotein-cholesterol. Meanwhile, Stamler and colleagues gave the percentage response of two drugs in black population as 32.7 and 15.1 percent respectively, but they failed to measure the metabolic response of these drug groups according to racial or ethnic factor. In another comparative study<sup>12</sup> in which the ethnicity of the patients was considered, Batey and colleagues observed that the differences between the decrease in TC and LDLC during prazosin therapy from the increases associated with hydrochlorothiazide therapy were significant in the white patients. Changes in TC and LDLC in black patients were similar but remarkably less and only significant for total cholesterol level. This observation suggests that ethnic factor may be important in the metabolism of cholesterol and its fractions during anti-hypertensive pharmacotherapy. Our study, which consisted of only Nigerians, shows a difference in response when compared with the profile in Caucasians or black Americans. Furthermore, Batey et al.<sup>12</sup> did not observe any significant differences in triglyceride and high-density lipoprotein cholesterol levels during prazosin and hydrochlorothiazide therapies in both black and white patients. Our data shows that the differences between decreases in LDLC, VLDLC and TO during doxazosin therapy and the increases during moduretic therapy were significant; in contrast to

other reported series<sup>11,12</sup>. In another comparative study involving nitrendipine and hydrochlorothiazide, serum cholesterol significantly increased with hydrochlorothiazide therapy, nitrendipine had no effect on lipid levels but high density lipoprotein cholesterol level did not change with either treatments. Again the study group here was made up of whites<sup>13</sup>. Amlodipine had no effect and moduretic adverse effect on lipid parameters in the present study. Overall, high-density lipoprotein cholesterol level was maintained in most of the reports in both black and white patients and this inert effect of anti-hypertensive agents on HDL cholesterol level was noted in Nigerian hypertensive patients as well. In conclusion, the cross-over study seems to confirm our previous reports on the monotherapies of these anti-hypertensive agents and thus demonstrates that doxazosin therapy is associated with favourable lipid and lipoprotein changes and moduretic therapy showed the opposite, while amlodipine therapy did not have any effect on the lipid parameters in African patients.

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