

Diuretics and β -Blockers Do Not Have Adverse Effects at 1 Year on Plasma Lipid and Lipoprotein Profiles in Men With Hypertension

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Background: Concern based on the reported short-term adverse effects of antihypertensive agents on plasma lipid and lipoprotein profiles (PLPPs) has complicated the therapy for hypertension.

Objective: To compare the long-term (1-year) effects of 6 different antihypertensive drugs and placebo on PLPPs in a multicenter, randomized, double-blind, parallel-group clinical trial in 15 US Veterans Affairs medical centers.

Patients and Methods: A total of 1292 ambulatory men, 21 years or older, with diastolic blood pressures (DBPs) ranging from 95 to 109 mm Hg taking placebo were randomized to receive placebo or 1 of 6 antihypertensive drugs: hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem, or prazosin. After drug titration, patients with a DBP of less than 90 mm Hg were followed up for 1 year. Plasma lipids and lipoprotein profiles were determined at baseline, after initial titration, and at 1 year.

Results: After 8 weeks on a regimen of hydrochlorothiazide,

increases of 3.3 mg/dL (0.09 mmol/L) in total cholesterol and 2.7 mg/dL in apolipoprotein B were significantly different ($P \leq .05$) from decreases of 9.3 mg/dL in total cholesterol and 5.4 mg/dL in ApoB levels while receiving prazosin but not from placebo. Patients achieving positive DBP control using hydrochlorothiazide (responders) showed no adverse changes in PLPPs, whereas nonresponders exhibited increases in triglycerides, total cholesterol, and low-density lipoprotein cholesterol levels. Plasma lipids and lipoprotein profiles did not change significantly among treatment groups after 1 year except for minor decreases in high-density lipoprotein 2 levels using hydrochlorothiazide, clonidine, and atenolol.

Conclusions: None of these 6 antihypertensive drugs has any long-term adverse effects on PLPPs and, therefore, may be safely prescribed. Previously reported short-term adverse effects from using hydrochlorothiazide are limited to nonresponders.

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ANTIHYPERTENSIVE drug therapy for systolic or diastolic hypertension, or both, has significantly reduced all-cause mortality, strokes, myocardial infarctions, and heart failure in morbidity and mortality clinical trials.¹ The regimens used in these trials were largely based on diuretic therapy and to a lesser extent on β -blockers.² In 1997, the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of Hypertension³ recommended that diuretics or β -blockers be considered as preferred initial drug therapy for the management of uncomplicated hypertension.

*For editorial comment
see pages 535 and 541*

In the United States, however, annual numbers of prescriptions for calcium channel blockers and angiotensin-

converting enzyme inhibitors now exceed prescriptions for diuretics and β -blockers. One of the reasons given for preferring these newer classes of antihypertensive agents has been the concern about the potentially detrimental effects of diuretics and β -blockers on plasma lipid and lipoprotein profiles (PLPPs).^{4,5} It is well known that, in addition to hypertension and smoking, proatherogenic alteration in PLPP is another major risk factor in the development of coronary heart disease.⁶ There are many reports on the short-term adverse effects of these drugs on PLPPs, but it is unclear whether these effects persist long-term. Furthermore, comparative PLPP changes in response to long-term therapy with commonly used

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PATIENTS AND METHODS

STUDY DESIGN

The study design has been described in detail previously.⁸ Briefly, ambulatory men (n = 1292) with diastolic blood pressures (DBPs) ranging from 95 to 109 mm Hg for 2 consecutive visits who met other entry criteria (see patient characteristics and exclusion criteria) after at least 4 weeks' placebo washout were randomized, stratified by participating site, to placebo or 1 of 6 drugs: hydrochlorothiazide (12.5-50 mg), atenolol (25-100 mg), captopril (25-100 mg), clonidine (0.2-0.6 mg), diltiazem-SR [short release] (120-360 mg), or prazosin (4-20 mg) daily. Compliance with the prescribed treatment regimen was assessed by pill count. Dose levels were titrated within these dose ranges until the goal DBP of less than 90 mm Hg for 2 consecutive visits or the maximum drug dose was reached. Patients who reached the goal blood pressure were advanced to a maintenance phase for at least 1 year.

PATIENT DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Characteristics of the study patients such as race, age, alcohol intake, systolic blood pressure and DBP, and exclusion criteria have already been reported.⁸ The criteria for inclusion were age of 21 years or older, written informed consent, and a reasonable expectation that the subject's DBP would be between 95 and 109 mm Hg with placebo.

EXCLUSION CRITERIA

Patients were excluded from the study if they had certain medical conditions listed elsewhere (NAPS Document No. 05006, NAPA c/o Microfiche Publications, New York, NY). Specifically with respect to lipid, lipoprotein, and glucose measurements, the patients with the

following characteristics were excluded from the study: (1) hyperlipidemia with plasma cholesterol levels higher than 300 mg/dL (7.7 mmol/L) in 2 separate plasma samples taken after at least a 12-hour fast or of sufficient severity to require treatment with medication, (2) symptomatic ischemic heart disease, (3) drug abuse or severe alcohol abuse, and (4) diabetes mellitus requiring insulin treatment.

PATIENT BLOOD COLLECTION

At each indicated visit, patients fasted for at least 14 hours prior to drawing of blood in lavender-topped tubes (EDTA: final concentration 1 mg/mL of blood). After separation, the plasma was stored in cryovials at -80°C in the central lipid laboratory, Veterans Affairs Medical Center, Washington, DC, where plasma lipid and lipoprotein analyses were carried out.

PLPP MEASUREMENTS

All lipid measurements were carried out with a clinical analyzer (VP Super System Clinical Analyzer using Abbott Agent Enzymatic Reagents; Abbott Laboratories, Abbott Park, Ill). The system was set up and standardized with the Centers for Disease Control and Prevention, Atlanta, Ga, quality control samples. If any quality control sample was not within 2 SDs of its mean, the entire batch of analysis was repeated. Previous experience showed that control pools were stable at -80°C for more than a year.

CHOLESTEROL DETERMINATION IN WHOLE PLASMA AND HIGH-DENSITY LIPOPROTEIN (HDL) SUBCLASSES

Plasma total cholesterol levels were determined using Abbott Agent Enzymatic cholesterol Reagents (Abbott Laboratories). Precipitation for the determination of HDL cholesterol and HDL3 cholesterol levels was performed

antihypertensive agents are not well established. To assess the short- and long-term effects of antihypertensive drugs on PLPPs, we report results from a randomized placebo-controlled trial of single-drug antihypertensive therapy in men with stage 1 or 2 diastolic hypertension. We also report the effects of antihypertensive therapy on serum potassium and glucose levels because of the known interactions between these 2 parameters, especially with respect to thiazide therapy.⁷

RESULTS

The number of patients randomized to each treatment group was as follows: hydrochlorothiazide, 188; atenolol, 178; captopril, 188; clonidine, 178; diltiazem, 185; prazosin, 188; and placebo, 187. Of these patients, 162 (86%) who were receiving hydrochlorothiazide had PLPP measurements at end titration, 147 (83%) for atenolol, 159 (85%) for captopril, 143 (80%) for clonidine, 151 (82%) for diltiazem, 137 (73%) for prazosin, and 154 (82%) for placebo. Differences among treatment groups concerning the numbers of patients available at end ti-

tration primarily reflect differences in dropout rates because of adverse drug effects. Medication compliance was 92% for prazosin and more than 95% for all other antihypertensive drugs.

Only patients achieving an adequate blood pressure response at end titration were eligible to enter the maintenance phase. The number of patients with PLPP values at 1 year who were receiving the following was hydrochlorothiazide, 78 (41%); atenolol, 84 (47%); captopril, 74 (39%); clonidine, 81 (46%); diltiazem, 95 (51%); prazosin, 66 (35%); and placebo, 41 (22%). Differences among treatment groups at 1 year reflect differences in the ability of the various treatments to reduce blood pressure during the titration phase.

COMPARISON OF TREATMENT GROUPS AT BASELINE

Comparison of baseline plasma biochemical parameters among the treatment groups revealed no significant differences at baseline. Mean values (SD) for all study patients were the following: total triglycerides, 135.3 (103.4)

according to established methods.⁹⁻¹¹ In case the plasma was highly lipemic, it was subjected to ultracentrifugation at 105 000g for 16 hours to remove the very low-density lipoprotein/chylomicron fraction before analysis for total cholesterol and HDL cholesterol. The intra-assay and interassay coefficients of variation for the various lipid parameters were, respectively, as follows: total cholesterol, 2.5% and 3.2%; HDL cholesterol, 3.5% and 6.7%; HDL3 cholesterol, 3.4% and 6.9%; and triglycerides, 2.2% and 4.3%.

PLASMA APOLIPOPROTEINS (Apo) A₁ AND B DETERMINATIONS

These were determined by highly specific and sensitive immunorate-nephelometric methods (ICS Nephelometer system; Beckman Instruments, Palo Alto, Calif) for the quantitative measurement of ApoA₁ and ApoB.^{12,13} The central lipid laboratory is standardized by the Centers for Disease Control and Prevention. The intra-assay and interassay coefficients of variation for the various Apo parameters were, respectively, as follows: ApoA₁, 3.5% and 7.2%; and ApoB, 4.3% and 7.8%.

SERUM POTASSIUM AND GLUCOSE

Serum potassium values were determined by flame photometry while the 12-hour fasting blood glucose level was determined by an automated clinical chemistry analyzer (Hitachi-Behringer Mannheim, Indianapolis, Ind).

STATISTICAL ANALYSIS

The sample size of 1292 was derived to assure sufficient statistical power to detect clinically relevant treatment differences in the primary outcome measure, which was the percentage of patients achieving a DBP of less than 90 mm Hg at end titration and maintaining DBP at less than 95 mm Hg through 1 year. This sample size was

also sufficient to detect differences between treatment groups in PLPPs of about 20%, considered to be a moderate treatment effect, with 90% power. Lipid, lipoproteins, potassium, and glucose parameters were compared at baseline across treatment groups using 1-way analysis of variance.¹⁴ If the 1-way analysis of variance *P* value was significant, all possible pairs of treatments were compared using the Tukey pairwise comparison procedure.¹⁴ In the tables, these differences are depicted by assigning a letter to each treatment group mean. Groups, which are significantly different by the Tukey procedure, do not share any assigned letters. Comparison of changes from baseline to end titration and changes from baseline to 1-year maintenance across treatment groups followed the analytical methods used for baseline comparisons. For each treatment group, changes from baseline to end titration and from baseline to 1-year maintenance were analyzed using the paired *t* test. The percentage of patients in each treatment group with clinically relevant PLPP values (total cholesterol, 240 mg/dL; LDL cholesterol, 160 mg/dL; and HDL cholesterol, <35 mg/dL) were compared at end titration and then at 1-year maintenance using the χ^2 test. Patients were classified at end titration as a blood pressure responder if their DBP was lowered to below 90 mm Hg for 2 consecutive visits. Responders to hydrochlorothiazide were compared with nonresponders by comparing changes from baseline to end titration using the 2 sample Student *t* test. Since the titration regimen allowed 2 increases in dosage to achieve blood pressure control, patients could have achieved blood pressure control using any of the 3 doses of each medication. Therefore, dose-related metabolic effects at the end of dose titration were examined using 1-way analysis of variance and Tukey pairwise comparison procedure.¹⁴ All analyses were performed using SAS statistical software version 6.¹⁵ All statistical tests were 2-sided and *P* ≤ .05 was the criterion for statistical significance.

mg/dL; total cholesterol, 204.5 (37.5) mg/dL; LDL cholesterol, 129.6 (37.1) mg/dL; HDL cholesterol, 48.4 (13.2) mg/dL; HDL2 cholesterol, 12.7 (9.8) mg/dL; HDL3 cholesterol, 35.8 (8.9) mg/dL; ApoA₁, 116.7 (26.4) mg/dL; and ApoB, 75.9 (20.3) mg/dL; serum potassium, 4.3 (0.4) mmol/L; and fasting glucose 106.6 (28.5) mg/dL (5.9 [1.5] mmol/L).

COMPARISON OF VARIOUS DRUG TREATMENT GROUPS FROM BASELINE TO END TITRATION

Changes in the PLPP

Changes in the PLPP for treatment groups are presented in **Table 1**. It was found that a decrease of 9.3 (27.3) mg/dL in total cholesterol after 8 weeks of receiving prazosin was significantly different (*P* ≤ .05) from an increase of 3.3 (31.9) mg/dL after hydrochlorothiazide treatment. Similarly, a decrease of 5.4 (18.4) mg/dL in ApoB while receiving prazosin differed significantly (*P* ≤ .05) from an increase of 2.7 (20.8) mg/dL after the

diuretic. There were no other differences between drugs during titration.

Serum Potassium and Glucose

A decrease of 0.38 (0.46) mmol/L in serum potassium levels after hydrochlorothiazide treatment was significantly different (*P* < .05) from changes for all other treatments. Similarly, an increase of 0.11 (0.42) mmol/L in serum potassium levels in the atenolol treatment group was significantly different (*P* < .05) from decreases of 0.05 (0.42) mmol/L and 0.04 (0.42) mmol/L in the prazosin and placebo groups, respectively. An increase of 6.7 (24.7) mg/dL in fasting glucose levels in the hydrochlorothiazide group was significantly different (*P* < .05) from no change (SD, 19.8) in the atenolol group, and decreases of 3.2 (21.5) mg/dL and 1.4 (18.3) mg/dL in the captopril and placebo groups, respectively. Similarly, an increase of 5.4 (21.6) mg/dL in fasting glucose levels in the clonidine group was significantly different from the above decreases in the captopril and placebo groups, respectively.

Table 1. Changes in Plasma Lipid and Lipoprotein Profiles and Other Metabolic Parameters at Baseline After Dose Titration*

Variable	Hydrochlorothiazide (n = 162)	Atenolol (n = 147)	Captopril (n = 159)	Clonidine (n = 143)	Diltiazem HCl (n = 151)	Prazosin (n = 137)	Placebo (n = 154)	P
Total triglycerides, mg/dL								
End titration	148.3 (100.4)	146.1 (89.9)	127.3 (114.6)	136.1 (140.7)	127.0 (89.8)	119.0 (68.1)	126.0 (76.1)	.05
Change from baseline	8.3 (70.5)	8.9 (76.0)	0.9 (93.6)	0.8 (111.3)	-3.5 (56.5)	-18.9 (74.5)	-11.6 (97.3)	
Total cholesterol, mg/dL								
End titration	210.9 (40.4)	202.9 (41.6)	203.1 (39.7)	200.3 (35.9)	204.6 (35.4)	197.2 (34.3)	204.9 (35.7)	.02
Change from baseline	3.3 A (31.9)	-3.5 AB (29.6)	-0.4 AB (26.3)	-0.8 AB (29.5)	-1.0 AB (27.5)	-9.3 B (27.3)	-0.6 AB (30.5)	
LDL cholesterol, mg/dL								
End titration	133.8 (40.4)	127.7 (38.7)	129.9 (35.1)	128.7 (34.5)	131.6 (34.2)	126.0 (35.3)	130.6 (35.3)	.16
Change from baseline	3.0 (31.0)	-3.3 (27.4)	0.4 (24.7)	0.1 (27.5)	-0.2 (28.3)	-5.3 (28.5)	2.1 (30.4)	
HDL cholesterol, mg/dL								
End titration	48.3 (12.7)	46.7 (12.6)	48.1 (13.3)	47.3 (12.6)	47.9 (13.8)	47.8 (12.0)	50.3 (14.2)	.59
Change from baseline	-0.1 (11.3)	-2.1 (12.0)	-0.3 (10.7)	-0.8 (11.5)	-0.0 (11.0)	-0.7 (10.5)	0.4 (9.4)	
HDL2 cholesterol, mg/dL								
End titration	12.2 (8.4)	12.1 (9.6)	12.7 (8.8)	12.6 (9.1)	12.0 (9.2)	12.9 (9.8)	14.0 (10.7)	.17
Change from baseline	-1.2 (10.9)	-1.0 (9.2)	0.1 (7.8)	-0.7 (9.9)	-0.7 (10.3)	0.9 (11.1)	1.4 (9.3)	
HDL3 cholesterol, mg/dL								
End titration	36.2 (8.9)	34.6 (7.3)	35.6 (9.7)	34.8 (7.6)	36.1 (8.6)	34.9 (9.4)	36.5 (10.1)	.07
Change from baseline	1.0 (8.3)	-1.0 (8.7)	-0.6 (9.2)	-0.1 (7.2)	0.9 (7.6)	-1.5 (7.8)	-0.8 (8.6)	
ApoA ₁ , mg/dL								
End titration	116.7 (27.4)	115.1 (27.6)	114.8 (24.2)	111.3 (23.9)	116.2 (26.9)	108.4 (23.9)	116.0 (22.7)	.28
Change from baseline	-0.1 (25.9)	-2.2 (26.6)	-2.2 (25.5)	-5.2 (25.4)	-0.3 (29.5)	-6.7 (23.3)	-2.6 (24.9)	
ApoB, mg/dL								
End titration	79.0 (19.8)	76.6 (22.1)	73.3 (21.1)	74.2 (20.9)	77.6 (19.9)	72.2 (19.0)	74.8 (19.7)	.02
Change from baseline	2.7 A (20.8)	-0.0 AB (20.7)	-1.2 AB (17.6)	-1.3 AB (19.2)	1.1 AB 1.2 (19.4)	-5.4 B (18.4)	0.5 AB (19.2)	
Serum potassium, mm								
End titration	3.93 (0.45)	4.44 (0.41)	4.35 (0.37)	4.34 (0.38)	4.29 (0.39)	4.23 (0.39)	4.30 (0.40)	<.001
Change from baseline	-0.38 C (0.46)	0.11 A (0.42)	0.06 AB (0.39)	0.05 AB (0.42)	-0.01 AB (0.42)	-0.05 B (0.42)	-0.04 B (0.42)	
Fasting glucose, mg/dL								
End titration	114.9 (37.9)	108.8 (28.3)	102.0 (22.3)	111.8 (26.7)	105.7 (24.1)	106.8 (29.8)	107.2 (31.7)	<.001
Change from baseline	6.7 A (24.7)	0.0 BC 1.0 (19.8)	-3.2 C (21.5)	5.4 AB (21.6)	1.7 ABC (14.4)	1.4 ABC (19.0)	-1.4 C (18.3)	

*LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and Apo, apolipoprotein. After an initial washout period of 4 weeks the subjects were randomized to placebo or 1 of 6 antihypertensive drugs. Plasma lipid and lipoprotein profiles were determined in the indicated number of veterans during baseline and at the end of titration phase visits as described in the "Subjects and Methods" section. To convert plasma lipid and lipoprotein profiles and glucose values into millimole equivalents multiply by 0.02586 and 0.05551, respectively. Values are mean (SD). All statistical tests were 2-sided and $P < .05$ was the criterion for statistical significance. Groups with differing letters (ie, A, B, C) were different from one another.

COMPARISON OF CHANGES IN PARAMETERS BETWEEN BASELINE AND AFTER TITRATION WITHIN EACH DRUG GROUP

Changes in the PLPP

The following decreases in values after titration with prazosin were significantly different from the baseline values: triglycerides, 18.9 (74.5) mg/dL ($P = .004$); LDL cholesterol, 5.3 (28.5) mg/dL ($P = .03$); HDL3 cholesterol, 1.5 (7.8) mg/dL ($P = .02$); ApoA₁, 6.7 (23.3) mg/dL ($P = .001$); and ApoB, 5.4 (18.4) mg/dL ($P < .001$). Clonidine therapy decreased ApoA₁ by 5.2 (25.4) mg/dL ($P = .02$).

Serum Potassium and Glucose

The various drugs caused the following changes after titration compared with baseline values: hydrochlorothiazide decreased serum potassium by 0.38 (0.46) mmol/L ($P < .001$); atenolol increased serum potassium by 0.11 (0.42) mmol/L ($P < .001$); captopril increased serum potassium by 0.06 (0.39) mmol/L ($P = .05$); and hydrochlorothiazide increased serum glucose by 6.7 (24.7) mg/dL ($P < .001$).

COMPARISON OF VARIOUS DRUG TREATMENT GROUPS FROM BASELINE AFTER 1-YEAR MAINTENANCE

Changes in the PLPP

Changes in PLPP from baseline to 1-year maintenance for the treatment groups are presented in **Table 2**. By pairwise comparison, an increase of 4.9 (11.3) mg/dL in HDL2 cholesterol in the placebo group was significantly different ($P \leq .05$) from decreases of 0.9 (14.6) mg/dL, 1.0 (9.6) mg/dL, and 2.7 (11.2) mg/dL in the hydrochlorothiazide, atenolol, and clonidine groups, respectively.

Serum Potassium and Glucose

A decrease of 0.31 (0.49) mmol/L in serum potassium in the hydrochlorothiazide group was significantly different from changes in all other groups. An increase of 8.2 (32.0) mg/dL fasting glucose in the hydrochlorothiazide group and an increase of 8.3 (28.7) mg/dL in the clonidine group were significantly different from a decrease of 4.5 (20.2) mg/dL in placebo group.

Table 2. Changes in Plasma Lipid and Lipoprotein Profiles and Other Metabolic Parameters After 1 Year of Dose Maintenance*

Variable	Hydrochlorothiazide (n = 78)	Atenolol (n = 84)	Captopril (n = 74)	Clonidine (n = 81)	Diltiazem (n = 95)	Prazosin (n = 66)	Placebo (n = 41)	P
Total triglycerides, mg/dL								
1-Year maintenance	148.7 (129.8)	155.8 (89.1)	147.7 (170.8)	129.2 (96.2)	126.2 (82.2)	117.8 (86.7)	126.8 (84.0)	.46
Change from baseline	10.5 (80.2)	14.6 (78.5)	17.7 (155.3)	2.2 (130.3)	5.5 (61.3)	-11.1 (61.1)	-17.8 (138.2)	
Total cholesterol, mg/dL								
1-Year maintenance	207.7 (36.4)	205.6 (40.2)	202.4 (33.7)	200.0 (39.9)	210.9 (39.5)	207.0 (39.9)	206.8 (33.1)	.81
Change from baseline	1.6 (33.7)	1.0 (35.6)	4.0 (25.0)	1.5 (33.0)	1.4 (34.1)	-3.8 (37.7)	-4.2 (37.1)	
LDL cholesterol, mg/dL								
1-Year maintenance	132.3 (40.1)	129.4 (38.7)	126.2 (33.2)	129.9 (39.3)	138.1 (36.4)	138.2 (40.9)	130.9 (35.8)	.75
Change from baseline	3.2 (36.8)	-0.1 (32.6)	-4.8 (26.4)	3.3 (30.1)	2.0 (32.6)	1.5 (42.4)	-2.1 (26.3)	
HDL cholesterol, mg/dL								
1-Year maintenance	47.6 (13.7)	46.1 (13.5)	48.2 (14.1)	46.4 (12.8)	48.7 (15.2)	46.5 (14.1)	52.6 (16.7)	.32
Change from baseline	-1.0 (12.4)	-2.9 (10.9)	-0.8 (8.6)	-3.1 (13.9)	-0.7 (9.6)	-2.5 (9.2)	1.6 (14.5)	
HDL2 cholesterol, mg/dL								
1-Year maintenance	13.3 (9.6)	12.2 (8.8)	13.0 (11.3)	12.0 (8.0)	13.0	13.5 (9.6)	16.5 (12.5)	.02
Change from baseline	-0.9 B (14.6)	-1.06 (9.6)	0.5 AB (10.5)	-2.7 B (11.2)	0.4 AB (9.6)	1.3 AB (7.6)	4.9 A (11.3)	
HDL3 cholesterol, mg/dL								
1-Year maintenance	34.4 (10.1)	34.1 (8.7)	35.8 (8.5)	34.5 (8.9)	35.8 (8.9)	33.1 (9.6)	36.1 (9.0)	.28
Change from baseline	-0.5 (9.1)	-1.9 (10.1)	-1.2 (10.0)	-0.4 (9.2)	-1.2 (8.0)	-3.8 (7.9)	-3.0 (10.4)	
ApoA ₁ , mg/dL								
1-Year maintenance	116.0 (28.0)	117.6 (28.8)	121.2 (30.0)	110.2 (24.0)	119.2 (29.0)	115.8 (30.2)	118.7 (25.3)	.23
Change from baseline	-1.9 (27.8)	0.1 (35.3)	2.4 (26.4)	-8.3 (25.7)	2.0 (29.3)	2.2 (31.2)	3.4 (35.6)	
ApoB, mg/dL								
1-Year maintenance	79.0 (22.4)	77.5 (22.0)	75.7 (21.3)	76.5 (20.2)	76.5 (19.9)	77.3 (17.6)	76.8 (17.6)	.76
Change from baseline	1.3 (24.2)	2.4 (21.6)	.7 (19.2)	3.8 (20.4)	0.2 (18.6)	-1.6 (21.4)	1.4 (14.9)	
Serum potassium, mmol/L								
1-Year maintenance	4.04 (0.47)	4.51 (0.43)	4.34 (0.34)	4.37 (0.39)	4.27 (0.35)	4.29 (0.34)	4A5 (0.37)	.001
Change from baseline	-0.31 B (0.49)	0.13 A (0.42)	-0.01 A (0.38)	0.09 A (0.42)	-0.02 A (0.45)	0.0 A (0.39)	-0.02 A (0.37)	
Fasting glucose, mmol/L								
1-Year maintenance	114.9 (45.9)	110.0 (32.0)	105.8 (25.2)	113.1 (37.9)	111.1 (32.5)	103.6 (15.7)	108.0	.006
Change from baseline	8.2 A (32.0)	0.6 AB (23.1)	-0.01 AB (16.9)	8.3 A (28.7)	5.0 AB (20.9)	-1.2 AB (24.7)	-4.5 B (20.2)	

*LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and Apo, apolipoprotein. After an initial washout period of 4 weeks the subjects were randomized to placebo or 1 of 6 antihypertensive drugs. Plasma lipid and lipoprotein profiles were determined in the indicated number of veterans during baseline and 1-year maintenance visits as described in the "Subjects and Methods" section. To convert plasma lipid and lipoprotein profiles and glucose values into millimole equivalents multiply by 0.02586 and 0.05551, respectively. Values are mean (SD). Statistical tests were 2-sided and $P < .05$ was the criterion for statistical significance. Groups with differing letters (ie, A and B) were different from one another.

COMPARISON OF CHANGES IN PARAMETERS BETWEEN BASELINE AND 1-YEAR MAINTENANCE WITHIN EACH DRUG GROUP

Changes in the PLPP

The following drugs caused indicated changes after 1-year maintenance compared with baseline values: atenolol decreased HDL cholesterol by 2.9 (10.9) mg/dL ($P = .02$); clonidine decreased HDL cholesterol by 3.1 (13.9) mg/dL ($P = .05$), and decreased ApoA₁ by 8.3 (25.7) mg/dL ($P = .005$). Prazosin decreased HDL3 cholesterol by 3.8 (7.9) mg/dL ($P < .001$); and placebo increased HDL2 cholesterol by 4.9 (11.3) mg/dL ($P = .01$).

Serum Potassium and Glucose

The various drugs caused the following changes after 1-year maintenance compared with baseline values: hydrochlorothiazide decreased serum potassium by 0.31 (0.49) mmol/L ($P < .001$), and increased serum glucose by 8.2 (32.0) mg/dL ($P = .02$). These changes in serum potassium and glucose in the thiazide group were sig-

nificantly different from changes in all other groups. Atenolol increased serum potassium by 0.13 (0.42) mmol/L ($P = .003$); clonidine increased serum potassium by 0.09 (0.42) mmol/L ($P = .04$); and increased serum glucose by 8.3 (28.7) mg/dL ($P = .006$). These increases in serum glucose in the diuretic and (α_2) agonist groups were significantly different from a decrease of 4.5 (20.2) mg/dL in the placebo group. Diltiazem increased serum glucose by 5 (20.9) mg/dL ($P = .01$).

CLINICALLY RELEVANT PLPP LEVELS AT END TITRATION AND 1-YEAR MAINTENANCE

Table 3 shows the percentage of patients in each treatment group with total cholesterol levels, more than 240 mg/dL; LDL cholesterol levels, 160 mg/dL or more; and HDL cholesterol levels, less than 35 mg/dL. Comparison of treatment groups at end titration shows a statistical trend ($P = .06$) for patients receiving hydrochlorothiazide to be more likely to have clinically relevant elevated total cholesterol levels. There is no difference among the treatment groups at 1 year.

Table 3. Clinically Relevant Plasma Lipid and Lipoprotein Profile Levels at End Titration and at 1-Year Maintenance*

Variable	Hydrochlorothiazide	Atenolol	Captopril	Clonidine	Diltiazem	Prazosin	Placebo	P
Total cholesterol \geq 240 mg/dL								
End titration	25.3	16.5	18.5	14.2	17.6	13.2	13.2	.06
1-Year maintenance	16.3	19.4	14.0	16.7	26.6	15.6	16.3	.31
LDL cholesterol \geq 160 mg/dL								
End titration	23.5	22.7	22.2	18.4	22.6	18.8	17.6	.14
1-Year maintenance	18.6	19.8	23.5	22.5	29.3	23.4	16.7	.55
HDL cholesterol $<$ 35 mg/dL								
End titration	10.2	13.9	13.0	8.1	13.2	11.1	5.7	.18
1-Year maintenance	15.1	16.7	8.3	12.4	11.3	13.0	8.3	.63

*Values are percentages. To convert total cholesterol values into millimole equivalents multiply by 0.02586. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

COMPARISON OF RESPONDERS VS THE NONRESPONDERS AT END TITRATION

Since treatment effects on PLPPs differed at end titration but not at 1-year maintenance, **Table 4** shows the changes in PLPPs at end titration for patients who responded to their assigned treatment (and were eligible for long-term therapy) and patients who did not respond (and were not eligible to proceed to the maintenance phase). Among patients assigned to the diuretic, total cholesterol values increased significantly in nonresponders compared with responders ($P = .02$) while the greater increase in triglyceride levels in nonresponders approached significance ($P = .06$). For patients receiving captopril, changes in total cholesterol levels comparing responders with nonresponders approached significance ($P = .06$). Among diuretic nonresponders, increases were seen for triglyceride levels, 21.8 (61.6) mg/dL ($P = .008$); total cholesterol levels, 10.9 (29.0) mg/dL ($P = .005$); and LDL cholesterol levels, 8.1 (27.4) mg/dL ($P = .02$). Atenolol responders had increased triglyceride levels (15.0 [78.5] mg/dL) ($P = .05$) and decreased HDL cholesterol levels (-2.5 [11.2] mg/dL) ($P = .03$). High-density lipoprotein 3 cholesterol levels decreased for nonresponders receiving clonidine (-3.4 [6.2] mg/dL). Nonresponders receiving prozosin had decreased total cholesterol levels (-7.7 [23.8] mg/dL) ($P = .05$) and ApoA₁ levels (-8.5 [21.5] mg/dL) ($P = .02$), while responders had decreased triglyceride levels (-19.0 [77.5] mg/dL), cholesterol levels (-9.9 [28.6] mg/dL) ($P < .001$), ApoA₁ levels (-5.9 [24.1] mg/dL) ($P = .02$) and ApoB levels (-6.5 [19.0] mg/dL) ($P < .001$).

CHANGES IN TOTAL CHOLESTEROL LEVELS BY HYDROCHLOROTHIAZIDE DOSE

Hydrochlorothiazide treatment caused dose-dependent changes in cholesterol levels during titration. Thus, in responders, cholesterol levels decreased by 6.2 mg/dL at 12.5-mg dosage, and increased by 2.7 mg/dL at 25- and 50-mg doses. In contrast, cholesterol levels increased by 11.2 mg/dL at the 50-mg dose in nonresponders.

Changes in Serum Potassium Levels by Hydrochlorothiazide

Potassium values decreased by 0.21, 0.34, and 0.5 mmol/L at 12.5-, 25-, and 50-mg doses, respectively, in responders.

Age, Medication Compliance, Change in Body Weight, Hematocrit, DBP, and SBP in the Hydrochlorothiazide Group

The mean (SD) age of nonresponders was 54.9 (12.8) years vs 60.8 (9.8) years for responders ($P < .001$). Compliance with the prescribed diuretic dosage was 98% (12%) in nonresponders vs 96% (12%) in responders ($P = .13$). There was no significant difference in body weight change in the 2 subgroups, which decreased by 0.85 (2.11) kg for responders and 0.45 (2.07) kg for nonresponders ($P = .40$). Nonresponders received 45.1 (11.1) mg of the diuretic compared with only 27.3 (16.3) mg ($P < .001$) in responders. The hematocrit change in nonresponders was 1.4 (2.6) compared with only 0.4 (3.6) for responders ($P = .03$). Responders showed a decrease in DBP of 14.2 (3.8) mm Hg compared with only a decrease of 5.1 (5.7) mm Hg in nonresponders ($P < .001$). Similarly, responders exhibited a decrease in SBP of 16.1 (8.4) compared with only 10.7 (12.7) mm Hg in nonresponders ($P = .001$).

COMMENT

Hypertension and hyperlipidemia are recognized as the major risk factors in the development of coronary heart disease as evidenced by a number of epidemiological studies throughout the world. Both may be affected by antihypertensive drug therapy. Previous studies¹⁶⁻²² have reported that some β -blockers and thiazide diuretics, while benefiting the patients in lowering hypertension, led to short-term increases in plasma triglyceride and LDL levels, but a decrease in HDL concentration. Thus, the seemingly opposite effects of these antihypertensive drugs are believed to account for their less than predicted benefit on coronary heart disease observed in some large intervention studies.¹⁶⁻²² Therefore, we have compared the 1-year effects of 6 antihypertensive drugs on PLPPs in men with stage 1 or 2 diastolic hypertension.

During the titration phase, the use of prazosin had significant beneficial effects in lowering plasma triglyceride, total cholesterol, LDL cholesterol, and ApoB levels (Table 1). Another study²³ also reported that this α -receptor antagonist caused significant decreases in plasma cholesterol and triglyceride levels. A previous study²¹ had shown that doxazosin, another α -receptor antagonist, decreased triglyceride levels by 5.9% and increased HDL cholesterol levels by 7.2%. A more recent report²² also confirms the favorable effects of this α -receptor antagonist on PLPPs. On the other hand, propranolol and atenolol, 2 of the β -adrenergic antagonists, were found to significantly increase triglyceride and decrease HDL cholesterol levels.²¹⁻²⁴ Our present study also shows that atenolol had a tendency to have adverse effects on triglyceride and HDL concentrations during the titration phase (Table 4).

A comparison of the plasma lipid parameters in responders vs the nonresponders to hydrochlorothiazide showed dramatic differences that were not seen for the other treatment groups (Table 4). Thus, the deleterious effects of hydrochlorothiazide in increasing plasma triglyceride, total cholesterol, and LDL cholesterol levels were found only in the nonresponders but not in the responders. These effects of hydrochlorothiazide in nonresponders compared with responders were neither due to noncompliance of drug use nor to lower diuretic dose. The forced up-titration to higher doses of hydrochlorothiazide probably accounts for its deleterious effects on PLPPs in nonresponders (Table 4). We suggest that these adverse effects of hydrochlorothiazide on PLPPs in nonresponders may be due to neuroendocrine stimulation. In contrast, hydrochlorothiazide has no significant adverse effects on PLPPs in responders (Table 4) and yet significantly lowers both DBP and SBP compared with nonresponders. Therefore, low-dose hydrochlorothiazide can be safely prescribed for long-term monotherapy of hypertension in responders.

The significant decrease in serum potassium at the end of titration and at 1 year of hydrochlorothiazide treatment is consistent with previous observations.²⁵⁻²⁷ Similarly, the occurrence of mild hyperglycemia after hydrochlorothiazide treatment confirms previous observations.^{7,19,28} Potassium depletion is known to be associated with impaired glucose tolerance.^{29,30} It is possible that the diuretic-induced hypokalemia may have caused hyperglycemia in these patients by interfering with the production of insulin, insulin resistance, or both. In contrast, the α_2 -agonist also caused mild hyperglycemia at the end of the titration period and at 1-year maintenance without any potassium depletion. Also, the β -blocker caused an increase in serum potassium levels at the end of titration, although this effect disappeared at 1-year maintenance. The exact mechanisms of action of these antihypertensive drugs on the regulation of potassium and carbohydrate metabolism remain to be elucidated.

Our results do not apply to patients with preexisting hypercholesterolemia or symptomatic coronary artery disease since these were reasons for exclusion from the study. In addition, women were not included in this study.

Table 4. Changes in Plasma Lipid and Lipoprotein Profiles From Baseline to End of Dose Titration Comparison of Responders and Nonresponders

Drugs	Blood Pressure Responder	Blood Pressure Nonresponder	P
Hydrochlorothiazide	(n = 102)	(n = 60)	
Total triglycerides	0.3 (74.4)	21.8 (61.6)	.06
Total cholesterol	-1.1 (32.8)	10.9 (29.0)	.02
LDL cholesterol	-0.0 (32.8)	8.1 (27.4)	.11
HDL cholesterol	-0.3 (11.8)	0.1 (10.5)	.83
HDL2 cholesterol	-1.7 (11.4)	-0.4 (10.0)	.48
HDL3 cholesterol	1.3 (8.6)	0.5 (7.9)	.56
ApoA ₁	0.8 (22.9)	-1.8 (30.5)	.54
ApoB	1.4 (21.4)	4.8 (19.9)	.33
Atenolol	(n = 107)	(n = 40)	
Total triglycerides	15.0 (78.5)	-7.5 (67.1)	.11
Total cholesterol	-3.7 (29.2)	-3.1 (31.0)	.92
LDL cholesterol	-4.0 (28.3)	-1.5 (25.2)	.62
HDL cholesterol	-2.5 (11.2)	-1.0 (13.8)	.51
HDL2 cholesterol	-1.4 (9.5)	-0.1 (8.4)	.47
HDL3 cholesterol	-1.2 (8.1)	-0.6 (10.0)	.69
ApoA ₁	-1.9 (25.9)	-3.0 (28.8)	.82
ApoB	-0.4 (22.3)	0.9 (15.9)	.72
Captopril	(n = 100)	(n = 59)	
Total triglycerides	2.2 (100.7)	-1.2 (80.9)	.83
Total cholesterol	-3.4 (26.9)	4.8 (24.6)	.06
LDL cholesterol	-2.3 (22.1)	4.8 (28.3)	.10
HDL cholesterol	-1.2 (8.4)	1.1 (13.7)	.26
HDL2 cholesterol	-0.2 (7.1)	0.6 (9.0)	.58
HDL3 cholesterol	-1.2 (9.1)	0.3 (9.4)	.35
ApoA ₁	-3.1 (20.0)	-0.6 (33.0)	.60
ApoB	-2.3 (16.7)	0.7 (19.1)	.30
Clonidine	(n = 108)	(n = 35)	
Total triglycerides	-6.0 (108.2)	21.9 (119.5)	.20
Total cholesterol	0.2 (28.9)	-3.9 (31.6)	.48
LDL cholesterol	0.6 (27.0)	-1.7 (29.5)	.68
HDL cholesterol	-0.3 (11.5)	-2.4 (11.5)	.35
HDL2 cholesterol	-1.3 (9.8)	1.1 (10.3)	.22
HDL3 cholesterol	-1.0 (7.2)	-3.4 (6.2)	.002
ApoA ₁	-4.0 (25.6)	-8.6 (24.7)	.35
ApoB	-1.2 (20.2)	-1.5 (16.2)	.93
Diltiazem	(n = 124)	(n = 27)	
Total triglycerides	-5.5 (54.4)	5.6 (65.8)	.36
Total cholesterol	-2.0 (28.0)	3.8 (24.8)	.32
LDL cholesterol	-0.9 (28.0)	3.0 (29.8)	.52
HDL cholesterol	0.1 (9.7)	-0.7 (15.9)	.80
HDL2 cholesterol	-0.2 (8.8)	-2.9 (15.3)	.38
HDL3 cholesterol	0.5 (7.5)	2.1 (8.0)	.30
ApoA ₁	-0.1 (31.4)	-1.4 (18.6)	.78
ApoB	0.6 (18.7)	3.5 (22.4)	.48
Prazosin	(n = 98)	(n = 39)	
Total triglycerides	-19.0 (77.5)	-18.7 (67.4)	.99
Total cholesterol	-9.9 (28.6)	-7.7 (23.8)	.68
LDL cholesterol	-5.8 (29.7)	-4.0 (25.6)	.76
HDL cholesterol	-0.8 (11.7)	-0.3 (6.7)	.79
HDL2 cholesterol	0.7 (12.0)	1.3 (8.3)	.76
HDL3 cholesterol	-1.5 (7.6)	-1.5 (8.3)	1.00
ApoA ₁	-5.9 (24.1)	-8.5 (21.5)	.56
ApoB	-6.5 (19.0)	-2.5 (16.6)	.25
Placebo	(n = 57)	(n = 97)	
Total triglycerides	-3.3 (118.5)	-16.5 (82.6)	.46
Total cholesterol	-4.6 (34.6)	1.8 (27.7)	.21
LDL cholesterol	0.1 (30.7)	3.2 (30.3)	.54
HDL cholesterol	-0.7 (9.3)	1.0 (9.5)	.29
HDL2 cholesterol	1.6 (7.2)	1.2 (10.3)	.80
HDL3 cholesterol	-1.9 (9.0)	-0.1 (8.3)	.21
ApoA ₁	-1.2 (26.7)	-3.4 (23.8)	.60
ApoB	-1.5 (19.2)	1.7 (19.1)	.33

*LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and Apo, apolipoprotein. Values are mean (SD). After an initial washout period of 4 weeks, the subjects were randomized to placebo or 1 of 6 antihypertensive drugs. Plasma lipid and lipoprotein profiles were determined in the indicated number of veterans during baseline and the end of titration phase visits as described in the "Subjects and Methods" section. All statistical tests were 2-sided and $P < .05$ was the criterion for statistical significance.

It is concluded from our study that none of the drugs had any significant adverse effects on any of the lipid parameters although hydrochlorothiazide and atenolol showed slight tendencies to cause short-term increases in triglyceride, cholesterol, and ApoB levels at the end of titration (Table 1). More important, the fact that all these lipid parameters were unaffected by any of the above-mentioned treatment drugs at 1 year strongly supports the conclusion that none of these drugs has any long-term adverse effects with respect to coronary heart disease. Furthermore, nondrug therapy, especially weight loss and exercise, can benefit both hypertension and PLPPs, when combined with antihypertensive drug therapy.²² Based on these findings, it is suggested that clinicians need not be overly concerned about PLPP effects while choosing any of the antihypertensive drugs for long-term therapy.

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