# Serum Lipoproteins During Treatment with the Antihypertensive Agent Indapamide

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**SUMMARY** **Considering the documented, potentially undesirable influence of various thiazide-type or loop diuretics on serum lipoproteins, we prospectively investigated in 69 men (mean age ± SEM, 32 ± 1 years) the metabolic effects of the new diuretic-antihypertensive compound indapamide. Compared to placebo, indapamide (2.5 mg/day) given for 6 to 8 weeks lowered ($p < 0.02$ to $< 0.001$) blood pressure (supine values from 148/98 ± 3/2 to 137/93 ± 3/2) in 29 men with mild to moderate essential hypertension, but not in 40 healthy men. In both groups, significant ($p < 0.05$ to $< 0.001$) decreases in body weight (−0.8 kg) and plasma potassium (−0.6 mmol/L), and increases in plasma uric acid (+20%), renin activity (+200%), and aldosterone documented good compliance. There were no significant changes in total cholesterol (in all subjects, from 208 ± 6 to 213 ± 6 mg/dl), low- or very low-density lipoprotein (VLDL) cholesterol (127 ± 6 to 129 ± 6 and 21 ± 1 to 21 ± 2 respectively), high-density lipoprotein cholesterol (50 ± 1 to 51 ± 1 mg/dl), total triglycerides (Tg) (108 ± 5 to 112 ± 6 mg/dl), VLDL-Tg, apoproteins A1 and A2, plasma glucose, epinephrine, norepinephrine, sodium, calcium, magnesium, and creatinine; apoprotein B (84 ± 2 to 88 ± 3 mg/dl) and plasma insulin after glucose loading dose tended to be increased minimally. The absence of distinct lipoprotein alterations after short-term indapamide treatment may be of clinical and epidemiological interest. (Hypertension 7 [Suppl II]: II-164–II-169, 1985)**

KEY WORDS • lipids • insulin • glucose • essential hypertension

DIURETICS have long been the major drugs in the treatment of hypertension. In recent years, however, some suspicion has arisen that, at least in some patients, their antihypertensive efficacy could be compromised by an undesirable influence on cardiovascular risk factor(s) other than blood pressure (BP).[1-3] One among several possibilities to be considered is lipoprotein metabolism. Based on epidemiological findings, decreases in high-density lipoprotein cholesterol (HDL-C) and increases in low-density lipoprotein cholesterol (LDL-C) may both augment the risk for coronary heart disease[4, 5]; a similar tendency is suspected for elevated blood levels of triglyceride (Tg)-rich lipoproteins.[6] Various diuretics may in fact modify potentially atherogenic lipoproteins.

Based on observations in this and other laboratories, various thiazide-type diuretics, when given for 1 month to 1 year, significantly increased LDL-C and/or very low-density lipoprotein cholesterol (VLDL-C).[7-12] Moreover, LDL-C was increased in diuretic-treated men and chlorthalidone-treated postmenopausal women, but not in chlorthalidone-treated premenopausal women.[13] The last may be protected from this effect. Also, HDL-C and, whenever measured, HDL's major apoproteins A1 and A2 (apo A1 and A2) were largely unchanged with thiazides.[12] This documents a frequent occurrence of elevated LDL-C/HDL-C and total C/HDL-C ratios in thiazide-treated men or postmenopausal women. Loop diuretics, such as furosemide, mefruside, and muzolimine, also increased these ratios due to mildly raised total or LDL-C and unchanged or even slightly decreased HDL-C values.[7, 12, 14-16] Moreover, slight increases in VLDL-Tg and/or total Tg were noted in most although not all[9, 10, 12, 14, 15] studies with thiazide-type or loop diuretics.

Whether these alterations in serum lipoproteins represent a metabolic side effect of all or only some types of diuretics has been unclear. Indapamide is a new

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diuretic-antihypertensive agent that differs from previous agents structurally[17] and possibly also in its vascular effects.[17, 18] A preliminary assessment in 18 men revealed stable levels of serum LDL-C and Tg after 6 weeks of indapamide treatment.[19] This called for the present extensive investigation of the metabolic effects of indapamide in a large and statistically representative group of 69 men.

## Subjects and Methods

Sixty-nine male subjects were studied. They included 40 normotensive men (mean age ± SEM, 28 ± 2 years) and 29 men with mild to moderate essential hypertension (mean age ± SEM, 37 ± 2 years). The normotensive subjects were healthy volunteers with BP consistently below 140/90 mm Hg. Mild to moderate hypertension was defined as diastolic BP ranging in the untreated state from 90 to 120 mm Hg. Secondary forms of hypertension were excluded by the usual tests. No patient had malignant hypertension (hypertensive retinopathy stages III–IV), edema, heart failure, stroke, or plasma creatinine level above 1.35 mg/dl. Any antihypertensive drugs were discontinued 4 weeks before the study. The subjects were instructed to maintain their usual diet but to avoid very salty foods. Physical activity was unchanged during study. Alcohol abusers were excluded. All subjects gave their informed consent.

In a single-blind approach, a matched placebo, 1 tablet every morning, was given for 4 weeks (placebo phase). The placebo was then replaced by active indapamide, 1 tablet (2.5 mg) daily for 6 to 8 weeks (mean treatment duration ± SEM, 7.7 ± 0.2 weeks). No other antihypertensive drug was added during the active phase.

At the end of the placebo and indapamide treatment phases, body weight was determined and measurements were obtained of BP; heart rate; serum total C, Tg, and lipoprotein fractions; plasma glucose (by the hexokinase method), insulin (by radioimmunoassay),[20] uric acid (by the uricase-phosphotungstate method; Hoffmann-La Roche Company, Basel, Switzerland); sodium, potassium (flame photometer), and chloride (by the thiocyanate method using Greiner selective analyzer GSA II; Greiner SA, Langenthal, Switzerland); magnesium (by atomic absorption), calcium (by fluorometric titration with ethylene glycol bis(B-aminoethyl ether)-*N,N,N',N'*-tetraacetic acid), and creatinine (Greiner autoanalyzer; Greiner SA, Langenthal, Switzerland); renin activity[21]; aldosterone[22]; epinephrine and norepinephrine levels[23, 24]; and urinary creatinine, sodium, and potassium excretion. The serum total lipids and lipoprotein fractions were determined twice within 1 to 4 days in the majority of the subjects (30 normotensive and 20 hypertensive men) and the mean of the two values was used for analysis. These measurements were always made between 0800 and 1000 hours after an overnight fast of at least 12 hours and 1 hour of rest in the supine position, as described previously from this laboratory.[8, 24] Blood pressure and heart rate were also measured in the upright position. Blood was collected through an intravenous cannula inserted into an antecubital vein at least 30 minutes before initial blood sampling.

In a subgroup of 30 normotensive and 13 hypertensive subjects, an oral load of 100 g glucose in water was administered after basal blood sampling, and plasma concentrations of glucose and insulin were determined 15, 30, 60, 120, and 180 minutes thereafter while the subjects remained in the supine position.

The lipoprotein fractions were isolated by sequential ultracentrifugation using standard methods.[25] The recovery of lipids in the isolated lipoprotein fractions was 90 to 92%. Apoproteins A1 and A2 were determined by solid-phase radioimmunoassay[26] and apo B by radial immunodiffusion[27] on commercial immunoplates (Partigen; Behring Werke, Marburg, West Germany). The coefficients of variation from day to day ($n$ = 10) were 4.5% for LDL-C, 3.5% for HDL-C, 7 and 9% for apo A1 and A2 respectively, and 6% for apo B. Isolated apo A1 and A2 were used as standards within each assay. In the case of apo B, a commercial standard (Behring Werke) was used. The assay sensitivities were below 10 ng for apo A1 and A2 and below 10 mg/dl for apo B. The distribution of serum lipoproteins was also determined by electrophoresis on agarose gel (Lipidophor system; Immuno SA, Vienna, Austria). Serum total C and total Tg were measured by Technicon AAII autoanalyzer (Technicon Corporation, Tarrytown, NY, USA).[28]

Statistical significance of differences between mean values were determined by Student's two-tailed paired $t$ test. Since natural logarithmic transformation rather than absolute values followed a gaussian distribution, the natural logarithmic transformations of plasma norepinephrine, epinephrine, renin activity, and aldosterone were used for statistical analysis.

## Results

### Clinical, Biochemical, and Endocrine Values

Compared to placebo conditions, 6 to 8 weeks of indapamide treatment significantly reduced supine and upright BP (−8%; $p < 0.02$ to $< 0.001$) and increased upright heart rate (+12%; $p < 0.001$) in the hypertensive group, while both values were largely unchanged in the normotensive subjects (Table 1). In both groups, indapamide slightly decreased body weight (−0.7 to −0.9 kg, $p < 0.05$ to $< 0.005$), lowered plasma potassium (−0.6 mmol/L; $p < 0.001$) and chloride ($p < 0.005$ to $< 0.001$), and increased plasma uric acid (+20%; $p < 0.001$), supine plasma renin activity (threefold; $p < 0.001$), and aldosterone ($p < 0.005$ to $< 0.001$) levels. Plasma sodium, calcium, magnesium, creatinine, and supine epinephrine and norepinephrine levels, as well as urinary sodium and potassium excretion rates and creatinine clearance, were not consistently modified after indapamide treatment.

Compared to placebo, indapamide therapy also did not significantly alter plasma volume in 21 hypertensive patients (100 ± 4 vs 100 ± 3% [SEM] of mean

TABLE 1. *Effect of Short-term Monotherapy with Indapamide on Various Clinical, Biochemical, and Endocrine Values (mean ± SEM)*

| | Normotensive subjects | | Hypertensive subjects | | All subjects | |
|---|---|---|---|---|---|---|
| | Placebo | Indapamide | Placebo | Indapamide | Placebo | Indapamide |
| Clinical values | | | | | | |
| *n* | 40 | | 29 | | 69 | |
| Age (yr) | 28 ± 2 | | 37 ± 2 | | 32 ± 1 | |
| Blood pressure (mm Hg) | | | | | | |
| Supine | 117/70 ± 2/1 | 113/71 ± 2/1 | 148/98 ± 3/2 | 137/93 ± 3*/2† | 130/82 ± 2/2 | 123/80 ± 2*/2 |
| Upright | 108/78 ± 2/1 | 106/77 ± 2/2 | 143/102 ± 2/2 | 129/96 ± 3*/2‡ | 123/88 ± 3/2 | 116/85 ± 2*/2§ |
| Heart rate (beats/min) | | | | | | |
| Supine | 63 ± 2 | 62 ± 1 | 69 ± 2 | 71 ± 2 | 66 ± 1 | 66 ± 1 |
| Upright | 85 ± 2 | 89 ± 2 | 85 ± 3 | 95 ± 3* | 85 ± 2 | 92 ± 2* |
| Body weight (kg) | 72.5 ± 1.3 | 71.6 ± 1.3‡ | 78.0 ± 1.9 | 77.3 ± 1.9§ | 74.8 ± 1.1 | 74.0 ± 1.1* |
| Biochemical values | | | | | | |
| Plasma sodium (mmol/L) | 141 ± 1 | 139 ± 0.5‖ | 138 ± 0.5 | 139 ± 0.5 | 140 ± 0.5 | 139 ± 0.5 |
| Potassium (mmol/L) | 4.2 ± 0.1 | 3.6 ± 0.1* | 4.2 ± 0.1 | 3.6 ± 0.1* | 4.2 ± 0.1 | 3.7 ± 0.1* |
| Chloride (mmol/L)¶ | 103 ± 1 | 99 ± 1* | 102 ± 1 | 99 ± 1‡ | 103 ± 0.5 | 99 ± 1* |
| Magnesium (mmol/L)¶ | 0.78 ± 0.02 | 0.79 ± 0.01 | 0.79 ± 0.01 | 0.77 ± 0.01 | 0.79 ± 0.01 | 0.78 ± 0.01 |
| Calcium (mg/dl)¶ | 9.1 ± 0.1 | 9.3 ± 0.1‖ | 9.2 ± 0.1 | 9.3 ± 0.1 | 9.1 ± 0.1 | 9.3 ± 0.1* |
| Creatinine (mg/dl) | 1.04 ± 0.02 | 1.08 ± 0.01 | 1.08 ± 0.02 | 1.09 ± 0.02 | 1.06 ± 0.01 | 1.08 ± 0.01 |
| Uric acid (mg/dl) | 5.6 ± 0.1 | 6.8 ± 0.2* | 6.1 ± 0.2 | 7.3 ± 0.2* | 5.8 ± 0.1 | 7.0 ± 0.1* |
| Urinary sodium (mmol/g creatinine) | 95 ± 8 | 112 ± 11 | 118 ± 7 | 131 ± 10 | 105 ± 6 | 120 ± 8 |
| Potassium (mmol/g creatinine) | 37 ± 2 | 45 ± 3 | 56 ± 5 | 58 ± 4 | 45 ± 3 | 50 ± 3§ |
| Creatinine clearance (ml/min/1.73 $m^2$) | 91 ± 4 | 90 ± 4 | 84 ± 5 | 85 ± 6 | 88 ± 3 | 88 ± 3 |
| Endocrine values | | | | | | |
| Supine plasma | | | | | | |
| Renin activity (ng/ml/hr) | 1.31 ± 0.17 | 3.51 ± 0.39* | 1.14 ± 0.13 | 3.76 ± 0.69* | 1.24 ± 0.11 | 3.62 ± 0.36* |
| Aldosterone (ng/dl) | 8.5 ± 0.8 | 14.6 ± 1.3* | 8.2 ± 0.8 | 13.8 ± 1.2‡ | 8.4 ± 0.6 | 14.3 ± 0.9* |
| Norepinephrine (ng/dl)¶ | 24.1 ± 1.8 | 33.1 ± 3.4 | 26.8 ± 2.8 | 27.7 ± 2.5 | 25.5 ± 1.7 | 30.2 ± 2.1 |
| Epinephrine (ng/dl)¶ | 4.3 ± 0.4 | 5.2 ± 0.8 | 4.9 ± 0.5 | 4.8 ± 0.4 | 4.6 ± 0.3 | 5.0 ± 0.4 |
| Glucose (mg/dl) | 93 ± 1 | 93 ± 1 | 97 ± 2 | 99 ± 2 | 95 ± 1 | 96 ± 1 |
| Insulin (mU/L) | 18.2 ± 2.1 | 15.5 ± 1.0 | 17.2 ± 1.4 | 17.7 ± 1.3 | 17.8 ± 1.3 | 16.7 ± 0.8 |

*$p < 0.001$ versus placebo.
†$p < 0.02$.
‡$p < 0.005$.
§$p < 0.05$.
‖$p < 0.01$.
¶Plasma chloride, magnesium, and calcium were determined in 30 normotensive and 20 hypertensive subjects, and norepinephrine and epinephrine in 26 and 30 of the subjects respectively.

normal value related to body surface area) and in 10 healthy subjects (101 ± 6 vs 111 ± 7%) so studied; similarly, hematocrit was stable in these hypertensive (45 ± 1 vs 46 ± 1%) and healthy subjects (45 ± 1 vs 45 ± 1%).

The fasting plasma levels of glucose and insulin were unchanged after indapamide treatment; values obtained after glucose administration tended to be slightly higher with indapamide, but this trend did not reach statistical significance except for plasma insulin 120 minutes after the loading dose (Figure 1).

### Serum Lipoproteins

Under placebo conditions, the hypertensive patients tended to have higher mean serum levels of total C, LDL-C, VLDL-C, total Tg, phospholipids, and apo B and a lower apo A1 value than the normotensive group (Table 2). Compared to placebo, total serum C or Tg as well as the lipoprotein composition were unchanged after 6 to 8 weeks of indapamide monotherapy in both groups, except for minimally higher apo B values.

Further analysis was applied to a subgroup of 12 patients whose BP became normal (mean supine BP < 107 mm Hg) during indapamide monotherapy, mean BP being decreased from 114 ± 1 to 99 ± 2 mm Hg ($p < 0.001$). Compared to placebo, inadapamide treatment again caused no significant changes in serum total C (219 ± 13 vs 225 ± 13 mg/dl), LDL-C (140 ± 11 vs 143 ± 11 mg/dl), VLDL-C (18 ± 2 vs 20 ± 3

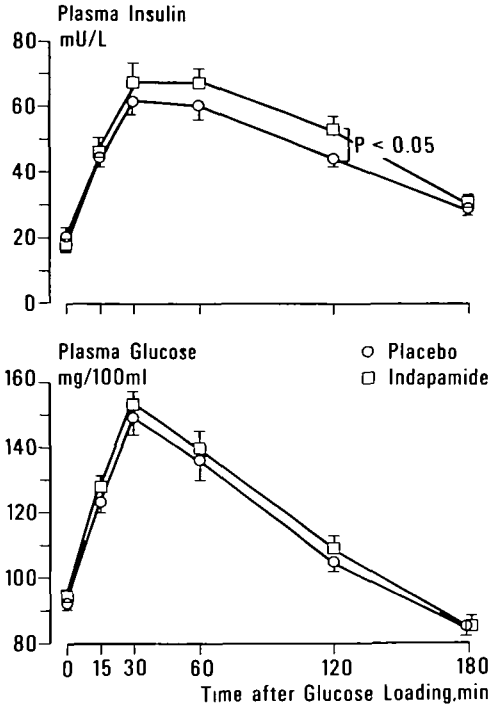


FIGURE 1. *Effect on plasma insulin and glucose of oral glucose loading before and after indapamide treatment in 43 men (mean values ± SEM). The* p *value denotes statistically significant difference between placebo and indapamide treatments.*

TABLE 2. *Effect of Short-term Monotherapy with Indapamide on Serum Lipoproteins (mean ± SEM)*

| | Normotensive subjects | | Hypertensive subjects | | All subjects | |
|---|---|---|---|---|---|---|
| | Placebo | Indapamide | Placebo | Indapamide | Placebo | Indapamide |
| *n* | 40 | | 29 | | 69 | |
| Serum cholesterol (mg/dl) | | | | | | |
| Total | 195 ± 6 | 201 ± 6 | 227 ± 10* | 229 ± 11 | 208 ± 6 | 213 ± 6 |
| Low-density lipoproteins | 119 ± 7 | 120 ± 7 | 140 ± 9 | 142 ± 9 | 127 ± 6 | 129 ± 6 |
| Very low-density lipoproteins | 18 ± 1 | 17 ± 1 | 25 ± 3 | 26 ± 4 | 21 ± 1 | 21 ± 2 |
| High-density lipoproteins | 50 ± 2 | 51 ± 2 | 50 ± 2 | 49 ± 2 | 50 ± 1 | 51 ± 1 |
| Serum triglycerides (mg/dl) | | | | | | |
| Total | 103 ± 7 | 101 ± 5 | 114 ± 8 | 127 ± 11 | 108 ± 5 | 112 ± 6 |
| Low-density lipoproteins | 20 ± 2 | 19 ± 1 | 18 ± 2 | 21 ± 2 | 19 ± 1 | 20 ± 1 |
| Very low-density lipoproteins | 56 ± 4 | 57 ± 3 | 60 ± 4 | 68 ± 8 | 58 ± 3 | 62 ± 4 |
| High-density lipoproteins | 25 ± 1 | 24 ± 2 | 31 ± 2 | 31 ± 3 | 28 ± 1 | 27 ± 2 |
| Serum phospholipids (mg/dl) | 187 ± 5 | 187 ± 5 | 209 ± 10† | 205 ± 8 | 196 ± 5 | 195 ± 5 |
| Serum alpha-lipoproteins (%) | 36 ± 2 | 36 ± 2 | 33 ± 2 | 33 ± 2 | 35 ± 1 | 35 ± 1 |
| Serum pre-beta-lipoproteins (%) | 11 ± 1 | 12 ± 1 | 13 ± 1 | 13 ± 1 | 12 ± 1 | 13 ± 1 |
| Serum beta-lipoproteins (%) | 53 ± 2 | 53 ± 2 | 54 ± 2 | 53 ± 2 | 53 ± 1 | 53 ± 1 |
| Serum apoproteins (mg/dl) | | | | | | |
| B | 80 ± 3 | 83 ± 3 | 91 ± 4† | 94 ± 5 | 84 ± 2 | 88 ± 3‡ |
| A1 | 123 ± 4 | 123 ± 4§ | 115 ± 4 | 117 ± 4 | 120 ± 3 | 120 ± 3‖ |
| A2 | 42 ± 1 | 43 ± 1§ | 40 ± 1 | 42 ± 2 | 41 ± 1 | 42 ± 1‖ |

*$p < 0.01$ versus placebo value of normotensive subjects.
†$p < 0.05$ versus placebo value of normotensive subjects.
‡$p < 0.02$ versus placebo.
§30 subjects.
‖20 subjects.

mg/dl), HDL-C (48 ± 2 vs 50 ± 2 mg/dl), total Tg (110 ± 8 vs 119 ± 12 mg/dl), VLDL-Tg (57 ± 6 vs 58 ± 9 mg/dl), apo A1 (110 ± 5 vs 111 ± 4 mg/dl), apo A2 (37 ± 2 vs 39 ± 2 mg/dl), or apo B (89 ± 6 vs 95 ± 6 mg/dl).

## Discussion

These findings demonstrated that treatment with the new diuretic-antihypertensive agent indapamide may be remarkably devoid of a potentially undesirable influence on serum lipoproteins. Compared to placebo, all measured lipoprotein C and Tg fractions were on the average unchanged after 6 to 8 weeks of indapamide monotherapy in a standard dose of 2.5 mg/day in 40 normotensive men, 29 men with mild to moderate essential hypertension, or all 69 men analyzed together; the major protein components of HDL, apo A1 and A2, also were unaltered, while LDL's major apo B tended to be increased only minimally. This constellation differs distinctly from the increase in the LDL-C/HDL and total C/HDL ratios induced by various thiazide-type or loop diuretics.[7-16]

The absence of lipoprotein alterations in our indapamide-treated men was not due to noncompliance with drug intake. In both the normotensive and hypertensive groups, significant ($p < 0.05$ to $< 0.005$) decreases in body weight (−0.7 to −0.9 kg), plasma potassium (−0.6 mmol/L) and chloride and increases in plasma uric acid (+20%), renin activity (threefold), and aldosterone levels documented drug actions also characteristic of some other classes of diuretics. Moreover, serum lipoprotein levels also were stable in the subgroup of hypertensive patients whose blood pressure was decreased to the normal range during indapamide therapy.

The broad metabolic profile of this study included in addition, plasma levels of calcium, magnesium, epinephrine, and norepinephrine, as well as glucose and insulin concentrations during fasting and after a standard oral glucose loading dose. These were not significantly changed after short-term indapamide treatment, except for a higher plasma insulin value 120 minutes after load. Others also noted largely unchanged plasma glucose levels in hypertensive patients after indapamide treatment for periods up to 40 weeks.[17, 29, 30] In our own previous studies, short-term monotherapy with the thiazide-type diuretics chlorthalidone or clopamide or the loop diuretics furosemide, mefruside, or muzolimine also did not consistently alter plasma catecholamine, glucose, and insulin values.[7, 8, 11, 13, 16]

It follows that, compared to indapamide, the contrasting influence of thiazide-type or some loop diuretics on serum lipoproteins can hardly be explained by a different effect on other metabolic values that were monitored in our studies. The course over time may play a role; however, the tendency for increases in the potentially atherogenic serum LDL-C (or LDL-C + VLDL-C) fraction or Tg concentrations was quite similar between 3 weeks and 12 months of monotherapy with thiazide-type or certain loop diuretics[12]; the duration of the present study was well within this period. On the other hand, it has to be considered that differences in the biochemical structure or dosages used could modify the influence of diuretic compounds on lipoprotein metabolism. The methyl-substituted isoindoline part of indapamide differentiates this agent structurally from previous thiazide-type or loop diuretics.[17] Spironolactone, which perhaps may also have little effect on serum lipoproteins,[31] differs structurally by its mineralocorticoid antagonism and effect on potassium metabolism. Compared to the standard antihypertensive dose of indapamide[17, 18, 29, 30] used in this study, relatively high daily doses of 100 mg chlorthalidone or hydrochlorothiazide were used in several investigations,[7-10, 12] but the similar increases in LDL-C and/or VLDL-C after high- or intermediate-dose (50 mg) chlorthalidone[9] or low-dose clopamide[11] provided no evidence for a major role of drug dosage. Nevertheless, whether and to what extent this side effect would also develop with a daily dose of chlorthalidone or hydrochlorothiazide as low as 25 mg is as yet unclear.

Indapamide appears to be a valuable alternative agent for diuretic-antihypertensive treatment.[17, 18, 29, 30] In our 29 patients with mild to moderate essential hypertension, BP was decreased significantly ($p < 0.02$ to $< 0.001$) after short-term indapamide monotherapy, from an average of 148/98 to 137/93 in the supine and to a similar extent in the upright position. Indapamide's antihypertensive effect occurs in the presence of unchanged blood volume, is associated with only a minimal decrease in exchangeable body sodium, and may be mediated at least in part by the lowering of abnormally high cardiovascular norepinephrine reactivity without an equivalent increase in adrenergic nervous activity.[18]

At the present stage, any of the lipoprotein changes induced by diuretics or other antihypertensive agents should be categorized as biochemical side effects and no more[12]; however, clarification of their possible pathogenic and prognostic relevance is needed. In the Multiple Risk Factor Intervention Trial,[2] the failure of coronary heart disease mortality to decrease in some patients receiving antihypertensive pharmacotherapy could not be explained by increased atherogenic serum lipoproteins. Although this points to other contributory factors, a disturbed lipoprotein metabolism, when it occurs, could nevertheless play a potentially aggravating role. Therefore it is of clinical interest that the new agent indapamide may allow effective diuretic-antihypertensive therapy and not cause unwanted changes in serum lipoproteins.

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