

## Effect of diuretics on the plasma lipid profile

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*Hypertension, dyslipidaemia, glucose intolerance (associated with insulin resistance and compensatory hyperinsulinaemia) and other abnormalities are complementary coronary risk factors which often occur in association. A familial trait for essential hypertension seems to coexist commonly with defects in carbohydrate and lipoprotein metabolism which can be detected before the appearance of hypertension. Diabetes mellitus as well as obesity promotes the development of hypertension and dyslipidaemia. Moreover, certain drugs used for antihypertensive therapy can further modify lipoprotein and glucose metabolism.*

*Thiazides in high dosage and loop-diuretics can increase serum low-density-lipoprotein cholesterol (LDL-C) and/or very-LDL-C and the total C/high-density lipoprotein cholesterol (HDL-C) ratio, while HDL-C is largely unchanged; triglycerides (Tg) are also often elevated. Premenopausal women may be protected from this side effect. Whether diuretic-induced dyslipidaemia is dose-dependent and low thiazide doses (i.e. hydrochlorothiazide  $\leq 12.5$  mg daily) are less active, awaits clarification. The diuretic-antihypertensive agent, indapamide, given at a dose of  $2.5 \text{ mg} \cdot \text{day}^{-1}$ , seems to exert no relevant effect on serum lipoprotein or glucose metabolism. The potassium-sparing diuretic, spironolactone, also may be largely neutral with regard to lipids. Moreover, potassium sparing diuretics may possibly counteract, at least in part, a dyslipidaemic influence of potassium-losing diuretics in medium dose.*

*Drug-induced dyslipidaemia, as well as glucose intolerance, represent potentially adverse influences. In the hypertensive population, effective blood pressure control with traditional drug therapy based on thiazide-type diuretics in high dosage led to a distinct decrease in cerebrovascular morbidity and mortality, but a lesser decrease in coronary events. The prognostic relevance of drug-induced metabolic changes such as dyslipidaemia, altered insulin sensitivity, and glucose intolerance awaits further clarification. It is of clinical interest that several of the generally available antihypertensive drugs seem to be metabolically 'neutral' or sometimes perhaps even potentially beneficial with regard to the lipoprotein and glucose metabolism.*

### Introduction

In the hypertensive population, high-dose diuretic therapy, with the older sympatholytics or the newer  $\beta$ -blockers as step two agents, and hydralazine-type vasodilators as step three agents, have lowered blood pressure effectively. Such therapy also improves overall cardiovascular and, in particular, cerebrovascular prognosis, but has had less benefit on the course of coronary heart disease and the incidence of sudden death<sup>[1-4]</sup>. In patients with mild hypertension, a diuretic monotherapy in high dosage reduced stroke but not the coronary complications, whereas monotherapy with the  $\beta$ -blocker propranolol slightly improved both the cerebrovascular and coronary prognosis in non-smokers, but failed to provide such benefit to smokers<sup>[5]</sup>. Suspicion has been growing that conventional antihypertensive therapy may unfavourably influence coronary risk factor(s) other than high blood pressure. Interactions with cardiac hypertrophy, electrolytes, carbohydrate and lipoprotein metabolism, angiotensin II, catecholamines, endothelial function and clotting factors are under particular consideration.

A decrease in high-density lipoprotein cholesterol (HDL-C) or increase in low density lipoprotein cholesterol (LDL-C) both augment the risk for coronary heart

disease<sup>[6]</sup>. A similar tendency is suspected for elevated blood levels of triglyceride (Tg)-rich lipoproteins, particularly when hypertriglyceridaemia is combined with a high LDL-C/HDL-C ratio<sup>[7,8]</sup>. In recent years it has become evident that several of the drugs used for standard antihypertensive therapy may interact with the lipoprotein metabolism<sup>[9-12]</sup>.

### Effects of diuretics

Thiazide-type diuretics, administered as a monotherapeutic regimen<sup>[9-11,13-30]</sup>, tend to increase serum total cholesterol (C) (reported average +4%), serum LDL-C (reported average +10%) (Fig. 1) as well as very low density lipoprotein cholesterol (VLDL-C). HDL-C (Fig. 1) and its major apoproteins A<sub>1</sub> and A<sub>2</sub> are on average unchanged. Thus, the LDL/HDL-C and total C/HDL-C ratios are frequently elevated. Loop diuretics, such as frusemide, mefruside, piretanide and muzolimine also tend to increase these ratios<sup>[9-11]</sup>. Moreover, slight increases in VLDL-triglycerides (VLDL-Tg) and/or total Tg (on average +9%) were noted in most, although not all studies with thiazide-type or loop-diuretics.

A critical aspect of any metabolic side effect is its course over time. Diuretic-induced dyslipidaemia persists for at least 1 year, with some studies documenting this alteration up to 6 years (Fig. 1). In the Multiple Risk Factor

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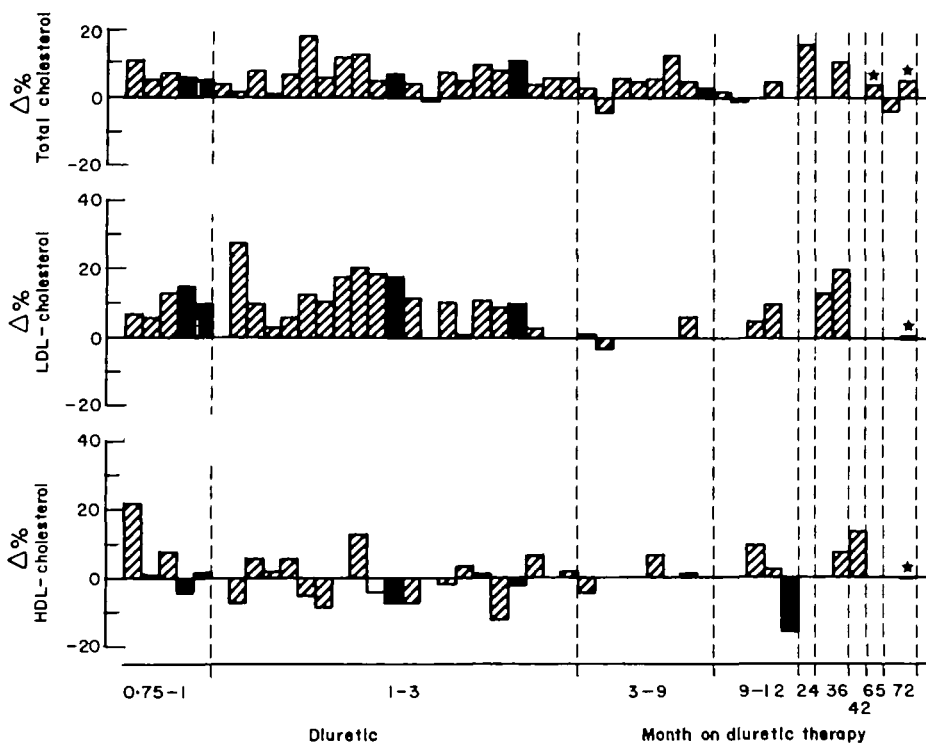


Figure 1 Percentage changes in serum total cholesterol, LDL-C and HDL-C in relation to the duration of a therapy with thiazide-type (hatched bars) or certain loop diuretics (closed bars);  $n \geq 10$  subjects per study. Asterisks denote differences between study groups on diuretics as compared with study groups on no diuretics or no antihypertensive drugs, see<sup>[23]</sup> and<sup>[26]</sup>. (Reproduced with permission<sup>[30]</sup>).

Intervention Trial (MRFIT)<sup>[23]</sup> and the Hypertension Detection and Follow-up Program (HDFP)<sup>[26]</sup>, a reduction in total cholesterol occurring in groups receiving no diuretics or any antihypertensive treatment, respectively, was blunted in groups receiving thiazide-type diuretics, even after 5 to 6 years of such monotherapy (Figs 2 and 3). In a further long-term study, cessation of hydrochlorothiazide (average dose  $51 \text{ mg} \cdot \text{day}^{-1}$ ) after a mean treatment duration of 5.2 years in 23 hypertensive patients resulted in a 7% decrease in total cholesterol and a 12% reduction in LDL-C<sup>[31]</sup> (Fig. 4).

Gender and the menopausal state may play a role in the interaction between diuretics and lipoproteins. In postmenopausal women, chlorthalidone administered in high dosage produced changes in serum total cholesterol and LDL-C similar to those in men; no changes were seen in premenopausal women<sup>[32]</sup> (Fig. 5). This points to a 'protective' influence of the premenopausal state. It seems that oestrogens increase the number of hepatic LDL-binding sites and stimulate the hepatic uptake of chylomicron-remnants<sup>[33]</sup>.

The development of dyslipidaemia may also be linked to the type and dose of the administered diuretics. The potassium-sparing diuretic, spironolactone, may be largely neutral with regard to plasma lipid levels<sup>[34-42]</sup> (Fig. 6), although reported data on LDL-C are scarce and those on HDL-C also too limited to allow a firm conclusion. Effects of a monotherapy with triamterene or amiloride on the plasma lipid profile are largely unknown, one

report describing a mild decrease in total C ( $-10\%$ ) after 7 weeks of amiloride treatment in 13 hypertensive men<sup>[43]</sup>.

Combinations of a potassium-losing diuretic (almost always a thiazide in medium dosage, for instance hydrochlorothiazide  $25-50 \text{ mg} \cdot \text{day}^{-1}$ ) with a potassium-sparing diuretic may be less prone to alter the lipoprotein metabolism than high-dose thiazides or loop-diuretics. A comprehensive analysis of reported studies reveals only minimal changes in serum total cholesterol and minor changes in total Tg on such combinations including either spironolactone ( $25-50 \text{ mg} \cdot \text{day}^{-1}$ ), triamterene (approximately  $20-100 \text{ mg} \cdot \text{day}^{-1}$ ) or amiloride ( $2-10 \text{ mg} \cdot \text{day}^{-1}$ )<sup>[11,44-58]</sup> (Fig. 7). As far as we know from reports, HDL-C tended to parallel total cholesterol<sup>[11,48,50,51,55,58]</sup>. Nevertheless, interpretation is somewhat limited due to incomplete information on gender and/or the menopausal state in some reports.

The diuretic-antihypertensive agent, indapamide, in the usual antihypertensive dose of  $2.5 \text{ mg} \cdot \text{day}^{-1}$ , does not produce dyslipidaemia<sup>[10,59]</sup>. (The methyl-substituted isoindoline part of indapamide differentiates this agent structurally from chlorthalidone, hydrochlorothiazide, furosemide and ticrynafen.) Compared with the rather low effective antihypertensive dose of indapamide, unnecessarily high daily doses of chlorthalidone, hydrochlorothiazide ( $50$  to  $100 \text{ mg} \cdot \text{day}^{-1}$ ) or other thiazides were generally utilized in studies focussing on interactions with lipoproteins as well as in the large therapeutic programmes in hypertensive patients.

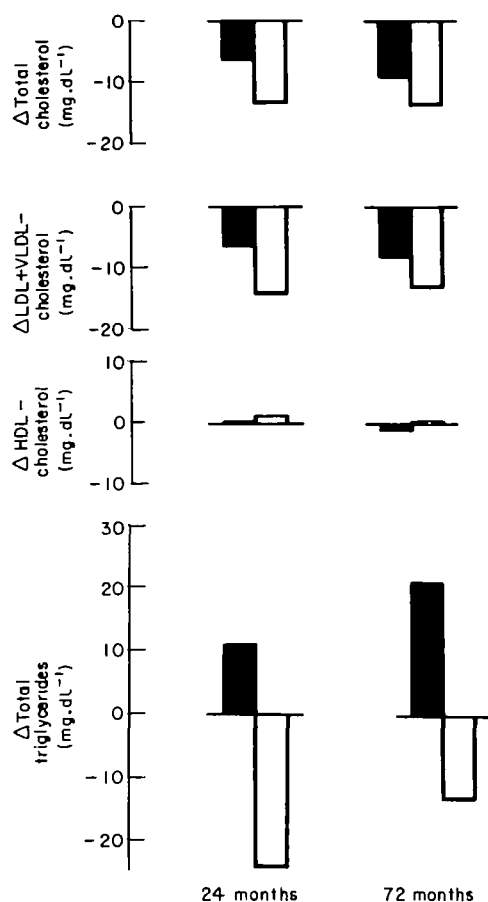


Figure 2 Absolute changes from baseline in serum total cholesterol, sum of LDL-C and VLDL-C and HDL-C (top) and in total triglycerides (bottom) in men in the MRFIT after 24 and 72 months of follow-up. All patients were on diet. Open bars represent patients without diuretics; closed bars, patients with diuretic therapy. (Data based on<sup>[23]</sup>).

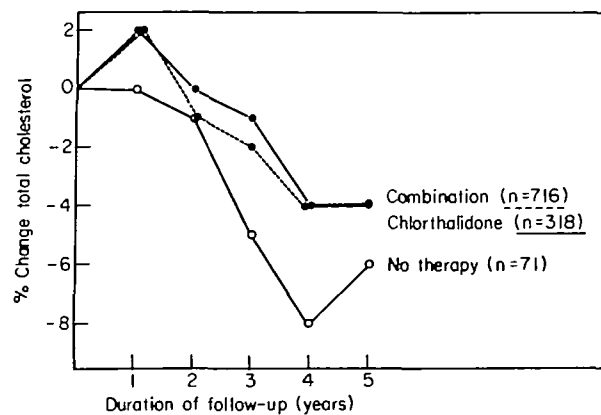


Figure 3 Percentage changes from baseline in serum total cholesterol of stepped care cohorts of patients on chlorthalidone therapy, combination therapy or no therapy, during a follow-up of 5 years in the Hypertension Detection and Follow-up Program. (Data based on<sup>[26]</sup>).

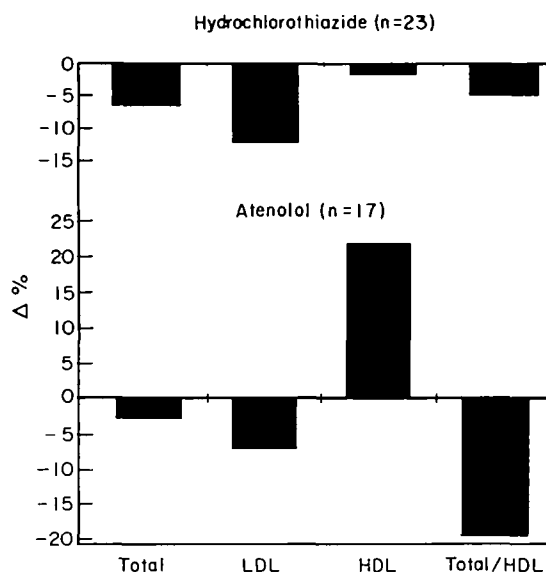


Figure 4 Percentage changes in serum cholesterol fractions 4-6 weeks after cessation of long-term antihypertensive treatment (mean duration 5.2 years) with the diuretic hydrochlorothiazide (average dose 51 mg . day<sup>-1</sup>; n = 23) or the  $\beta$ -blocker atenolol (average dose 75 mg . day<sup>-1</sup>; n = 17). Changes in total triglycerides were +4% or -14% after discontinuation of hydrochlorothiazide or atenolol, respectively. (Data based on<sup>[31]</sup>).

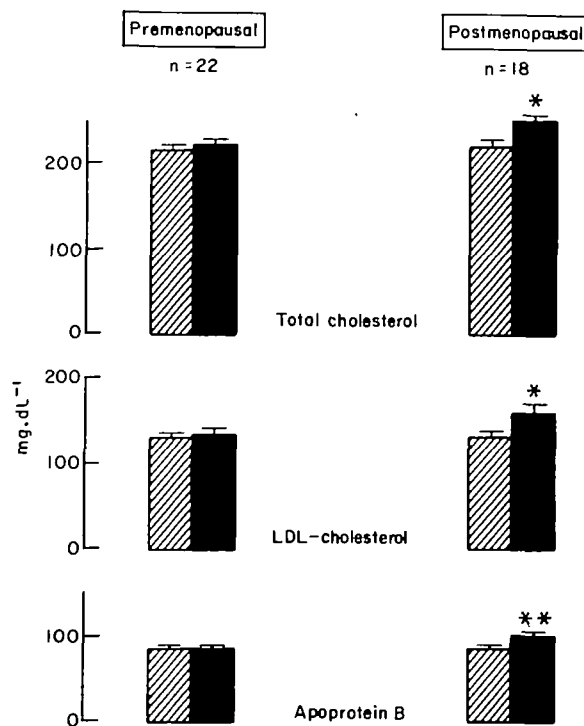
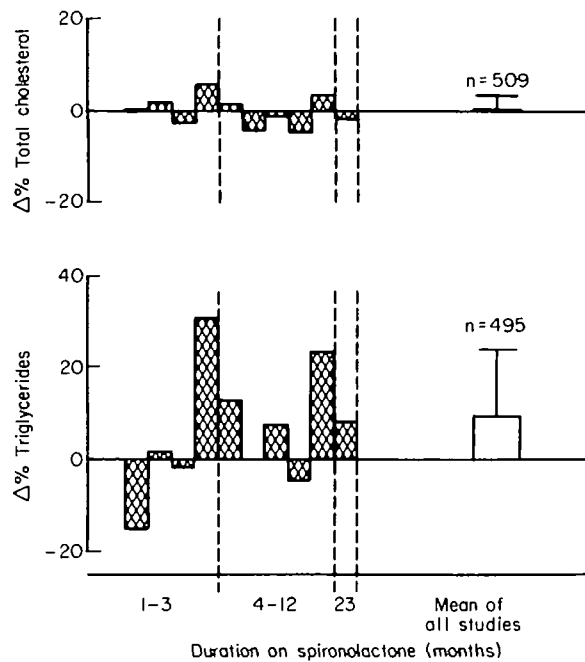
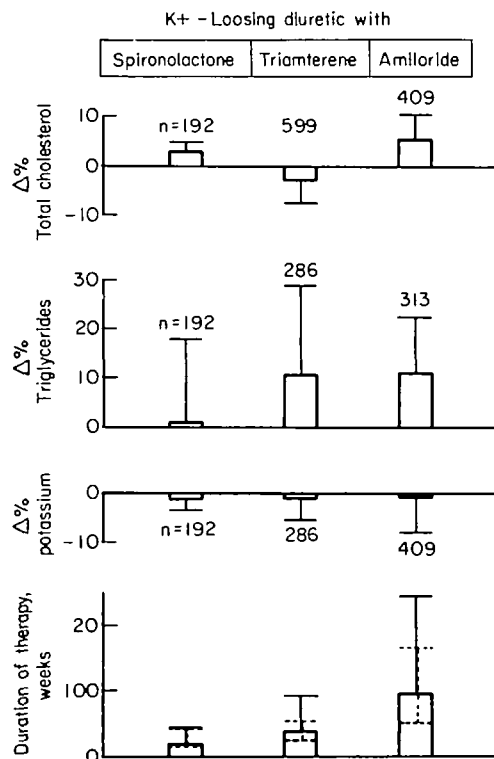


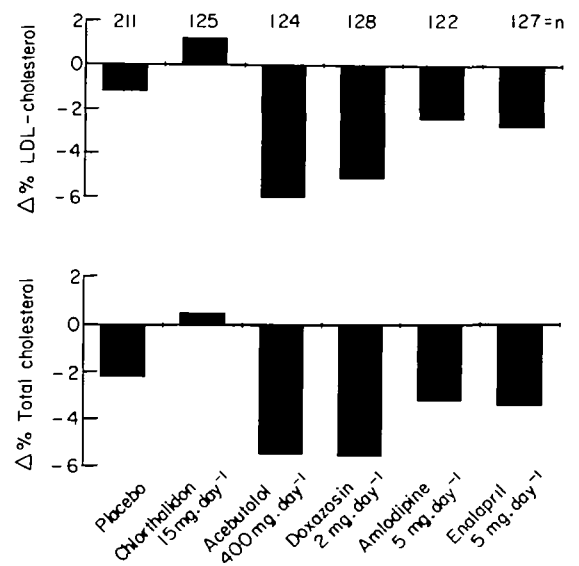
Figure 5 Effect of treatment with chlorthalidone in high dosage (100 mg . day<sup>-1</sup>  $\times$  6 weeks) on serum total cholesterol, LDL-cholesterol and apoprotein B in pre- or postmenopausal women. Mean values  $\pm$  SEM are shown. The P values denote statistically significant differences between placebo (▨) and chlorthalidone treatment (■); \* = P < 0.001; \*\* P = 0.05. (Data based on<sup>[27]</sup>).



**Figure 6** Percentage changes in serum total cholesterol and triglycerides in relation to the duration of a monotherapy with spironolactone.  $n \geq 13$  subjects per study. Average changes in all reported subjects are given as mean  $\pm$  SD.



**Figure 7** Average percentage changes in serum total cholesterol, triglycerides and potassium in reported studies using combinations of a potassium-losing diuretic (almost always thiazides) with a potassium-sparing diuretic. Mean  $\pm$  SD. There were no significant differences between combinations including either spironolactone, triamterene or amiloride.



**Figure 8** Percentage changes in serum total and LDL cholesterol after 1 year of therapy with different types of agents in the Treatment of Mild Hypertension Study. (Data based on<sup>[63]</sup>).

Since effects of thiazides on serum potassium, glucose and uric acid are dose-dependent, in low doses they may be also less prone to modify the lipoprotein profile<sup>[60]</sup>. Nevertheless, similar increases in serum total cholesterol and LDL-C were noted in hypertensive men receiving during up to 42 months either  $< 50$  or  $> 50$  mg hydrochlorothiazide daily<sup>[27]</sup>, in nine subjects treated during  $\geq 6$  months with hydrochlorothiazide, 50 mg  $\cdot$  day<sup>-1</sup>, and then during 6 months 25 mg  $\cdot$  day<sup>-1</sup><sup>[61]</sup>, or in nine postmenopausal women receiving during subsequent 1 month periods 12.5 as compared with 112.5 mg hydrochlorothiazide daily<sup>[62]</sup>. On the other hand, measurements in patients with mild hypertension (average age 55 years, 38% women) after 1 year of therapy with nutritional-hygienic intervention combined with different types of antihypertensive drugs revealed that low dose chlorthalidone (15 mg  $\cdot$  day<sup>-1</sup>) was associated with minimal increases in total cholesterol (+0.5%) and LDL-C (+1%), whereas administration of placebo or drugs thought to be neutral with regard to total and LDL-C (amlodipine, enalapril) were accompanied by mild decreases in total cholesterol (-2 to -3%) and LDL-C (-1 to -3%) (Fig. 8). Nevertheless, changes in HDL-C/total cholesterol ratio did not differ significantly between low-dose chlorthalidone (+5%) and the other treatments (+8 to +10%) (Fig. 9)<sup>[63]</sup>.

#### Possible mechanisms

The mechanisms of diuretic-induced dyslipidaemia are still unclear. Nevertheless, diuretics, particularly when administered in high dosage, can slightly increase sympathetic nervous activity<sup>[64]</sup> and/or levels of circulating norepinephrine. This may, in turn, promote lipolysis<sup>[65]</sup>, stimulate the hepatic synthesis of cholesterol subsequently secreted as VLDL and probably also raise the

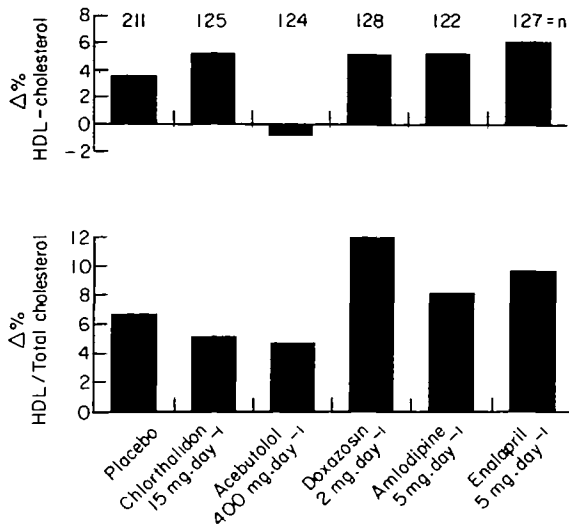


Figure 9 Percentage changes in serum HDL cholesterol or the HDL/total cholesterol ratio after 1 year of therapy with different types of agents in the treatment of mild hypertension study. (Data based on<sup>[63]</sup>).

atherogenic serum cholesterol fraction. Dependence of the latter on noradrenergic modulation is suggested by a positive correlation between plasma norepinephrine and LDL + VLDL-C both before and after sympathetic neurone blockade in patients with essential hypertension or renal failure<sup>[66]</sup>. Thiazide-type and loop diuretics can also impair insulin sensitivity<sup>[67]</sup>. Changes in potassium may possibly play a role in this interaction<sup>[53]</sup>. The latter and/or the resulting compensatory hyperinsulinaemia are known to promote hypertriglyceridaemia, a tendency for low HDL-C, and atherogenesis<sup>[68]</sup>. It can be hypothesized that, with intact lipoprotein lipase activity, excess VLDL could be metabolized to LDL-C, thereby contributing perhaps also to increased total serum cholesterol concentration.

#### Other antihypertensive agents

Several  $\beta$ -blockers tend to increase Tg and decrease HDL-C. These changes are most prominent on unselective  $\beta_{1+2}$ -blockers without intrinsic sympathomimetic activity (ISA), less pronounced on selective  $\beta_1$ -blockers without ISA, discrete on  $\beta$ -blockers with modest ISA and largely absent on  $\beta$ -blockers with pronounced ISA<sup>[9,12]</sup>. Some  $\beta$ -blockers can also slightly reduce insulin sensitivity and/or secretion and during long-term treatment impair glucose tolerance, particularly when they are administered in combination with diuretics<sup>[30]</sup>. Celiprolol, a  $\beta_1$ -blocker with concomitant  $\beta_2$ -agonism and  $\alpha_2$ -antagonism, tends to decrease Tg and increase HDL-C<sup>[36]</sup>.

Considering combination treatment, diuretic-induced increases in LDL-C may, at least in the short-term, be prevented by the concomitant administration of certain  $\beta$ -blockers<sup>[69,70]</sup>.

Postsynaptic  $\alpha_1$ -blockers can slightly decrease Tg, LDL-C and the total C/HDL-C ratio, while insulin

sensitivity, insulin secretion and glucose tolerance may tend to be improved<sup>[12,30]</sup>. Some other sympatholytics are largely neutral with regard to lipoproteins and glucose tolerance.

ACE inhibitors, calcium channel blockers and the serotonin<sub>2</sub>-receptor blocker ketanserin do not adversely affect serum lipoproteins<sup>[12,30,71]</sup>. ACE inhibitors tend to decrease serum total Tg and slightly improve insulin sensitivity and glucose tolerance<sup>[30]</sup>. The latter has been largely unchanged in clinical studies of calcium channel blockers or ketanserin; nevertheless, whether or not clinical treatment with such agents can produce subtle changes in insulin sensitivity or secretion is presently unclear.

#### Relevance and outlook

Whether the lipoprotein changes induced by certain antihypertensive drugs can per se modify the long-term prognosis of patients so treated is still unclear. In patients with high serum cholesterol concentration (pre-treatment  $C > 6.5 \text{ mm} \cdot \text{l}^{-1}$ ), long-term C-lowering with either diet or drugs produced a 1.5% decrease in coronary heart disease for every 1% reduction in serum cholesterol. Whether this correlation also holds for both decreases and increases from initially normal or mildly elevated serum cholesterol levels is not yet known. Therefore, attempts to calculate a potential impact of diuretic-induced increases in serum total cholesterol and LDL-C on coronary prognosis would be speculative.

Whatever the relative contribution of dyslipidaemia, diuretic therapy may concomitantly aggravate several potential cardiac risk factors, including impaired insulin sensitivity with compensatory hyperinsulinaemia, electrolyte imbalance, sympathetic and angiotensin II-stimulation, and others. Although it has been difficult to demonstrate a primary preventive effect of  $\beta$ -blockers on coronary prognosis, such agents, and particularly those without ISA, have been found to be effective at least in the secondary prevention of myocardial infarction. Therefore,  $\beta$ -blockers may possibly have a beneficial effect on some key steps involved in atheroma formation<sup>[72,73]</sup>. It follows that diuretics and  $\beta$ -blockers have done at least 'some good', while a prognostic efficacy of newer drug classes, such as calcium channel blockers, ACE-inhibitors, postsynaptic  $\alpha_1$ -blockers and  $S_2$ -blockers remains to be demonstrated.

Finally, it is important to note that observations on interactions of antihypertensive agents with lipoproteins have so far been limited largely to serum concentrations. However, lipid binding to vascular cells, the uptake, concentrations and metabolic processes in vascular cells rather than in the blood stream are decisive for atherogenesis, and effects of the different antihypertensive agents at the cellular level remain to be investigated. Therefore, possible differential indications for the various antihypertensive drugs are only beginning to emerge. Still, at this stage, it is of clinical interest that several of the generally available antihypertensive drugs seem to be metabolically 'neutral' or sometimes perhaps even potentially beneficial with regard to the lipoprotein and glucose metabolism.

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