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REVIEW ARTICLE

Thiazides, beta blockers and lipoproteins

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Introduction

Beta blockers and thiazide diuretics are the most commonly used agents in the treatment of hypertension because of their efficacy and lack of side effects. It is hoped that by lowering blood pressure with these drugs the medium and long-term risk of coronary heart disease is reduced. The Veterans Administration Cooperative Group (1970) provided clear evidence of an effect on cerebrovascular disease morbidity and mortality, but a decrease in cardiac events was not proven. More recently, encouraging evidence of such a reduction in coronary heart disease mortality has been reported by the Hypertension Detection and Follow-up Program Cooperative Group (1979a, b). However, the authors considered that the data for cause of death were too unreliable to permit conclusions to be drawn. It therefore seems that therapy of hypertension is more effective in reducing cerebrovascular disease than coronary heart disease.

Since it is known that plasma lipoprotein concentrations are more strongly associated with coronary heart disease than cerebrovascular disease (Ballantyne *et al.*, 1974), it is possible that agents which adversely affect plasma lipoproteins may have a greater influence in reducing benefit in coronary heart disease than in cerebrovascular disease. With the exception of free fatty acids, lipids are transported in plasma complexed with specific apoproteins as lipoproteins. There are 4 major classes of lipoproteins: chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). Chylomicrons are rarely present in fasting serum and will not be discussed. Epidemiological studies have indicated that elevated LDL and reduced HDL concentrations are associated with an increased risk of coronary heart disease (Kannel, Castelli and Gordon, 1979; Heiss *et al.*, 1980). It is therefore important to examine the effects of drugs commonly used in the treatment of hypertension on these lipoproteins.

The purpose of this paper is to review present knowledge concerning the relationship between beta-blockers, thiazide diuretics and lipoprotein concentrations.

Thiazide diuretics and lipoproteins

Schoenfield and Goldberger (1964) reported that thiazide diuretics adversely affected serum cholesterol concentrations, but their study was not followed up for about a decade. Some of the more recent studies are shown in Table 1. Ames and Hill (1976a, b) showed that 6 months' treatment with the thiazide-related diuretic chlorthalidone, which, like thiazide diuretics, acts on the distal tubule, was associated with a rise in plasma triglyceride and cholesterol. Interpretation of their findings was complicated by the prescription of a salt-restricted diet to all patients. Twenty-five of the 32 patients in the chlorthalidone-treated group received a calorie-restricted diet and 27 received a lipid-lowering diet. A number of other studies have been published concerning the effect of up to 6 months therapy on plasma lipids. Grimm *et al.* (1981) confirmed the elevation in plasma triglycerides and cholesterol but Gluck *et al.* (1980), Bauer *et al.* (1981) and Meier *et al.* (1982) found no significant changes. In one report, 6 weeks treatment with chlorthalidone produced a rise in VLDL- and LDL-cholesterol, whereas with hydrochlorothiazide, only VLDL-cholesterol was increased (Grimm *et al.*, 1981). The rise in LDL-cholesterol has been confirmed in other investigations of short-term therapy with thiazide diuretics (Gluck *et al.*, 1980); Meier *et al.*, 1982), but no rise in VLDL was observed and, in the study of Gluck *et al.* (1980), there was a fall in HDL.

Each of the lipoprotein classes consists of a series

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TABLE 1. Effect of hydrochlorothiazide (H) and chlorthalidone (C) on plasma lipoproteins

Study	n (drug)	Plasma Lipids		Lipoprotein		Chol	Apoproteins		Duration
		TG	Chol	VLDL	LDL	HDL	ApoAI	ApoB	(weeks)
Ames and Hill, 1976a	32 (C)	↑	NS	—	—	—	—	—	26
Ames and Hill, 1976b	25 (C)	↑	↑	—	—	—	—	—	26
Goldman *et al.*, 1981	610 (C)	↑	↑	—	↑	NS	—	—	52
Gluck *et al.*, 1981	37 (C)	NS	NS	NS	↑	↓	NS	NS	6
Grimm *et al.*, 1981	60 (C)	↑	↑	↑	↑	NS	—	—	6
Meier *et al.*, 1982	18 (C)	NS	NS	NS	↑	NS	—	—	6
Helgeland *et al.*, 1978a	26 (H)	NS	NS	—	—	NS	—	—	208
Helgeland *et al.*, 1978b	72 (H)	NS	NS	—	—	—	—	—	156
Van Brummielen, 1979	10 (H)	NS	↑	—	—	NS	—	—	36
Grimm *et al.*, 1980	60 (H)	↑	↑	↑	NS	NS	—	—	6
Bauer *et al.*, 1981	13 (H)	NS	NS	NS	NS	NS	—	—	4

Abbreviations: TG = triglyceride; Chol = cholesterol; VLDL = very low density lipoproteins; LDL = low density lipoproteins; HDL = high density lipoproteins; — = not analysed; NS = no significant difference; ↑ = significantly increased; ↓ = significantly decreased.

of particles containing both lipid and apolipoproteins. Apolipoprotein-B (apoB) is the major protein component of LDL and apolipoprotein-AI (apoA1), the predominant protein in HDL. From a study of myocardial infarction survivors and control subjects, Avogaro *et al.* (1979) concluded that apoAI and apoB concentrations may be as effective discriminators for risk of coronary heart disease as total cholesterol and triglyceride concentrations in subjects less than 50 years old and to be better discriminators in older subjects. Gluck *et al.* (1980) measured apoB and apoAI in their study of chlorthalidone. Despite a rise in LDL-cholesterol, no change in apoB was found and the authors suggested that this indicated that the LDL particle had become enriched in cholesterol but that the number of LDL particles had not increased. The authors speculated that this effect on LDL might be mediated through an effect on the liver. ApoAI was also not significantly altered despite a fall in HDL-cholesterol concentration. The authors did not suggest an explanation for this discrepancy.

There are also conflicting results of the effect of long-term therapy, i.e. for greater than 6 months. Two reports of the effect of hydrochlorothiazide after 4 years (Helgeland, Hjermann and Leren, 1978a) and after 3 years (Helgeland *et al.*, 1978b) showed no significant change in plasma triglyceride, total cholesterol or HDL-cholesterol. More recently, Goldman *et al.* (1980) reported that when chlorthalidone was given to 610 patients with mild hypertension for 1 year, there were significant increases in plasma total triglyceride and cholesterol concentrations, together with a significant elevation of LDL-cholesterol. No change in HDL was found and results for VLDL were not presented.

There is no obvious explanation for the discrepancies in the results of the above studies. Compliance has rarely been assessed and may be a problem particularly in long-term studies. It is likely that there may have been differences in the quality assurance programmes operated by the participating laboratories.

In summary, no firm conclusions can be drawn as to the effect of long-term therapy with hydrochlorothiazide or chlorthalidone on plasma lipids or lipoproteins. Treatment probably does cause an acute change in the lipoprotein profile. The most consistent changes are increases in plasma total triglyceride and cholesterol concentrations together with an increase in LDL-cholesterol. Since only one report found a significant fall in HDL-cholesterol (Gluck *et al.*, 1980), it is unlikely that thiazide diuretics significantly affect this lipoprotein.

Both hydrochlorothiazide and chlorthalidone promote sodium and water excretion. Their principal sites of action are the upper part of the ascending limb of the loop of Henle and the beginning of the distal tubule. The mechanism by which these drugs alter the lipoprotein concentrations is not clear. Lipoproteins are not found normally in tubular fluid, because they are too large to be filtered by the normal glomerulus. Even when the glomerular membrane suffers extensive damage as in the nephrotic syndrome, only HDL escapes into the filtrate. We are aware of no evidence of effects of either hydrochlorothiazide or chlorthalidone on lipoprotein metabolism in, for example, liver or gut. The age of the patient was not considered to be a factor (Goldman *et al.*, 1980). Haematocrit and albumin changes have been reported to be small and insufficient to explain the short-term changes in lipoproteins (Grimm *et al.*, 1981). However, one study of the effect of 6–24 months' therapy with thiazides reported persistent plasma volume contraction (Tarazi, Dustan and Frohlich, 1970). Thus, it is possible that, changes in plasma volume may be important in long-term studies. It is interesting, but unexplained that in one report (Goldman *et al.*, 1980), there was an inverse relationship between the change in plasma cholesterol and the baseline cholesterol concentration.

Apart from the study of Gluck *et al.* (1980), in which apoB and apoAI were estimated, there is little evidence on the effects of thiazide diuretics on apolipoproteins or on HDL subfractions. HDL_2 has been shown to be significantly reduced in patients with established coronary heart disease whereas no change was found in HDL_3 (Ballantyne *et al.*, 1982). It is possible that an alteration in the proportion of these 2 subfractions, which may influence risk of atherosclerosis, could be induced by therapy with or without a significant alteration in total HDL-cholesterol. Further research on these aspects is required.

Beta-adrenoceptor blocking agents and lipoproteins

A summary of papers published in the last decade is given in Table 2. Eight subjects with elevated fasting plasma triglyceride levels, who received a 60 g fat meal before and after 3 weeks treatment with propranolol showed an enhanced lipaemic response to the meal after the therapy (Barboriak and Friedberg, 1973). The data also suggested a small, but not statistically significant, increase in fasting plasma triglyceride levels after only a 2-week exposure to the drug. This rise in plasma triglyceride was not confirmed by Tanaka *et al.* (1976) who gave propranolol for 8 weeks to 10 patients who had suffered cerebrovascular accidents. However, despite the lack of a significant change in total triglyceride, there was a significant rise in VLDL-triglyceride, which was accompanied by falls in LDL-triglyceride and in HDL-cholesterol concentrations. Post-heparin lipolytic activity was significantly suppressed by propranolol and the authors considered that inhibition of lipoprotein lipase by propranolol might have played a role in the reciprocal changes in lipoprotein lipids. There have been 4 more recent studies of the effect of propranolol therapy (see Table 2). The duration of treatment ranged from 4 (Bauer *et al.*, 1981) to 24 weeks (Day *et al.*, 1979). In one study, however, the length of treatment was not reported (Streja and Mynin, 1978). Two of the four studies (Day *et al.*, 1979; Leren *et al.*, 1980) reported a significant increase in plasma triglyceride, and none showed a significant change in plasma total cholesterol. In 3 of these studies, HDL-cholesterol was analyzed (Streja and Mynin, 1978; Leren *et al.*, 1980; Bauer *et al.*, 1981) but in only 2 were significant falls in HDL recorded (Streja and Mynin, 1978; Leren *et al.*, 1980). In contrast to the report by Tanaka *et al.* (1976), VLDL and LDL concentrations were unchanged in the studies of Leren *et al.* (1980) and Bauer *et al.* (1981). The results of the short-term effects of propranolol on plasma lipoprotein concentrations are therefore conflicting. Although, as will be discussed later, there have been some long-term studies on the effect of combined therapy with propranolol and a thiazide diuretic on lipoprotein levels, no such studies of propranolol monotherapy have been conducted.

Propranolol is a non-cardioselective beta-adrenoceptor blocking agent without intrinsic sympathomimetic activity (ISA). One might therefore expect other drugs with this mechanism of action to cause similar changes in lipoproteins. Sotalol is one such agent, which was investigated by Lehtonen and Viikari (1979). They studied the effect of this drug over 1 year and found major alterations in the lipid profiles of their patients. There were significant rises in plasma total triglyceride and cholesterol with an accompanying increase in VLDL- and LDL-cholesterol and a fall in HDL. Their study lasted longer than the previously cited reports concerning propranolol but the design was comparable in other ways. It emphasizes the need for further long-term studies of propranolol. Labetolol is also a non-cardioselective beta-adrenoceptor blocking drug without ISA, but which possesses significant alpha blocking activity. In a 3-week study, Sommers *et al.* (1981) found that labetolol produced a significant fall in plasma total cholesterol without significantly altering plasma triglyceride or HDL-cholesterol. Thus, a review of the literature concerning the non-cardioselective beta-adrenoceptor blocking agents without ISA does not reveal a consistent effect.

It has been shown that, in adipose tissue, the lipid mobilizing effect of catecholamines is mediated through stimulation of the beta-adrenergic receptors (Smith, 1980), particularly the β_1 receptors with the β_2 receptors having a lesser influence. The α_2 receptors of this tissue probably mediate an anti-lipolytic action (Wright and Simpson, 1981). If the action of a beta-adrenoceptor blocking drug on plasma lipids is mediated through adipose tissue beta receptors, one might therefore expect cardioselective drugs, which are mainly β_1 adrenoceptor blocking agents, to have a different and lesser effect than the non-cardioselective agents. The liver has an important role in lipoprotein metabolism. We are not aware of any report of the effects of beta blockers on this organ. Most studies to date have been performed on readily accessible blood cells and adipocytes (Motulsky and Insel, 1982).

The cardioselective agents atenolol and metoprolol have been extensively studied. Four reports concerning metoprolol and 3 of atenolol have been reviewed (Table 2). Only the study of Eliasson, Lins and Rossner (1981) lasted for longer than 6 months. Three groups reported an increase in plasma triglyceride (Waal-Manning, 1976; Day *et al.*, 1979; England *et al.*, 1980), but 4 found no significant change (Nilsson, Hannson and Hokfelt, 1977; Beinart *et al.*, 1979; England *et al.*, 1980; Eliasson *et al.*, 1981). In none of these studies was a rise in plasma total cholesterol found. England *et al.* (1980), who investi-

gated both metoprolol and atenolol over 12 weeks, found that they produced a fall in HDL-cholesterol, whereas Eliasson *et al.* (1981) found no change in this lipoprotein after 32 weeks of atenolol therapy. The latter authors, however, reported increased VLDL- and LDL-triglyceride concentrations.

The presence of cardioselectivity therefore does not appear to produce more consistent changes than those found with non-selective beta blockers. Where significant changes were found they were similar to those reported with non-selective agents, i.e., a rise in plasma triglyceride and a fall in HDL-cholesterol. As with non-selective drugs, there is a paucity of long-term studies, only one being conducted for more than 6 months (Eliasson *et al.*, 1981). There is an obvious need for more such investigations.

A further property of some beta-adrenoceptor blocking agents, which might influence the effect on plasma lipoproteins, is the presence of ISA. Oxprenolol has ISA, but pindolol has significantly greater ISA. In a 3-week investigation of oxprenolol, Sommers *et al.* (1981) reported a significant decrease in plasma total cholesterol with no change in plasma triglyceride or HDL (VLDL and LDL concentrations were not measured). In contrast, Ballantyne, Ballantyne and McMurdo (1981) found significant rises in plasma total and LDL-cholesterol after 16 weeks of therapy. No change was found in plasma triglyceride, VLDL-cholesterol or HDL-cholesterol. The explanation for this discrepancy may lie in differences in the duration of the studies and in differences in lipoprotein methodology and possibly in quality assurance. It has recently been suggested by Lehtonen *et al.* (1982) in a 26-week study that pindolol significantly lowers plasma total cholesterol and raises HDL-cholesterol. However, the rise in HDL was only significant at 1 month. These effects of pindolol require confirmation.

TABLE 2. Effect of therapy with beta-adrenoreceptor blocking agents on plasma lipoproteins

Type of beta-adrenoreceptor blocking drug / Study	Number	Plasma Lipids		Lipoprotein			Duration (weeks)	Drug
		TG	Chol	VLDL	LDL	HDL		
Non-cardioselective agents without ISA								
Baboriak and Friedberg, 1973	8	NS	NS	—	—	—	2	Propranolol
Tanaka *et al.*, 1976	10	NS	NS	↑TG	↓TG	↓Lip	8	Propranolol
Stretja and Mynin, 1978	37	NS	NS	—	—	↓	Not given	Propranolol
Day *et al.*, 1979	16	↑	NS	—	—	—	24	Propranolol
Lehtonen and Viikari, 1979	12	↑	↑	↑	↑	↓	52	Sotalol
Leren *et al.*, 1980	23	↑	NS	NS	NS	↓	8	Propranolol
Sommers *et al.*, 1981	80	NS	↓	—	—	NS	3	Labetolol
Bauer *et al.*, 1981	10	NS	NS	NS	NS	NS	4	Propranolol
Cardioselective agents without ISA								
Waal-Manning, 1976	14	↑	NS	—	—	—	12	Metoprolol
Nillson *et al.*, 1977	9	NS	NS	—	—	—	12	Metoprolol
Day *et al.*, 1979	14	↑	NS	—	—	—	24	Atenolol
Beinart *et al.*, 1979	15	NS	NS	—	—	—	12	Metoprolol
Leren *et al.*, 1980	34	↑	NS	—	—	↓	12	Metoprolol
England *et al.*, 1980	34	NS	NS	—	—	↓	12	Atenolol
Eliasson *et al.*, 1981	15	NS	NS	↑TG	↑TG	NS	32	Atenolol
Non-cardioselective agents with ISA								
Ballantyne *et al.*, 1981	9	NS	↑	NS	↑	NS	16	Slow Oxprenolol
Sommers *et al.*, 1981	80	NS	↓	—	—	NS	3	Oxprenolol
Lehtonen *et al.*, 1982	20	NS	↓	—	—	↑	26	Pindolol
Cardioselective agents with ISA								
Ghosh *et al.*, 1975	20	NS	NS	—	—	—	52	Practolol

Abbreviations given in Table 1.

TABLE 3. Effect of combined therapy with thiazide diuretics and beta-adrenoceptor blocking agents on plasma lipids and lipoproteins

Study	Number	Plasma Lipids		Lipoprotein			Duration (weeks)	Drugs
		TG	Chol	VLDL	LDL	HDL		
Helgeland *et al.*, 1978	33	↑	NS	—	—	↓Chol	208	Hydrochlorothiazide and Propranolol
England *et al.*, 1978	18							Chlorothiazide and
		↑	NS	—	—	—	4	Atenolol* or
		↑	NS	—	—	—	4	Metoprolol* or
		↑	NS	—	—	—	4	Pindolol† or
		↑	NS	—	—	—	4	Propranolol
Crisp *et al.*, 1980	13	NS	NS	—	NS	NS	8	Cyclopenthiazide and Slow Oxprenolol†
Kristenson, 1981	51	NS	NS	—	—	NS	216	Hydroflumethiazide and Propranolol
Ballantyne *et al.*, 1981	11	↑	NS	↑TG	NS	NS	16	Cyclopenthiazide and Slow Oxprenolol†
Bauer *et al.*, 1981	11	↑	NS	↑TG	NS	NS	16	Hydrochlorothiazide and Propranolol

Abbreviations given in Table 1. *Cardioselective; †With intrinsic sympathominetic activity.

In summary, therefore, the literature concerning the effect of beta-adrenoceptor blocking agents on plasma lipoproteins is conflicting. No consistent differences arise from the presence of cardioselectivity or ISA. In this regard, it is relevant that the one study involving the cardioselective drug practolol which also possesses ISA (Ghosh, Cochrane and de Bono, 1975), showed no significant changes in plasma lipids following 12 months treatment. There are few studies lasting more than 6 months and since these drugs are usually prescribed on a long-term basis, further investigations are obviously required.

Combined therapy with beta-adrenoceptor blocking drugs and thiazide diuretics

Results from 5 recent studies are presented in Table 3. Four of the investigations use a thiazide diuretic and propranolol. A significant increase in plasma triglyceride without alteration in plasma cholesterol was found by Helgeland *et al.* (1978a), England, Hua and Shaw (1978) and Bauer *et al.* (1981). In one study, a significant fall in HDL-cholesterol was found (Helgeland *et al.*, 1978a) but in 2 this lipoprotein was unchanged (Kristenson, 1981; Bauer *et al.*, 1981). Only in one were VLDL and LDL analyzed (Bauer *et al.*, 1981) and a rise in VLDL-triglyceride concentration was found. The results of this latter trial were similar to those reported by Ballantyne *et al.* (1981) who investigated combined therapy with slow oxprenolol and cyclopenthiazide but contrast with the report by Crisp *et al.* (1980) who found no increase in total triglyceride on this combined therapy. England *et al.* (1978) also reported increases in plasma triglyceride following 4 weeks therapy with chlorothiazide and atenolol or pindolol or metoprolol.

Unlike the literature dealing with monotherapy with either thiazides or beta-adrenoceptor blocking drugs, reports on combined therapy are reasonably consistent. The main effect is a rise in plasma triglyceride with only one study reporting a fall in HDL-cholesterol. This is rather surprising in view of the known reciprocal relationship between plasma triglyceride and HDL-cholesterol concentrations (Ballantyne, Olsson and Carlson 1978a, b).

Summary

Some of the more important recent studies on the effect of thiazides and beta-adrenoceptor blocking agents on plasma lipoproteins have been reviewed. The evidence for an effect of monotherapy with either thiazide or beta-adrenoceptor blocking agents is conflicting, possibly because of differences in patient compliance and in lipoprotein methodology and quality assurance between studies. It is likely that in the short-term, thiazide diuretics produce an increase in plasma triglyceride and cholesterol and in LDL-cholesterol. No consistent effect of monotherapy with beta-adrenoceptor blocking agents was seen. Further long-term studies of monotherapy with both of these classes of drugs are required. Combined therapy with thiazides or beta-adrenoceptor blocking agents consistently increased plasma triglyceride concentrations, but their effect on VLDL, LDL and HDL concentrations is uncertain. Further research is required into the effect of these drugs on apolipoproteins which may be useful discriminators for patients with coronary heart disease (Avogaro *et al.*, 1979) and on HDL subfractions.

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