Medical Progress

The Effects of Diuretics and Adrenergic-Blocking Agents on Plasma Lipids

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Antihypertensive medications cause the following changes in plasma lipids and lipoproteins: Thiazide and loop diuretics increase triglyceride, total cholesterol and low-density-lipoprotein (LDL) cholesterol levels with no change in high-density-lipoprotein (HDL) cholesterol. β-Adrenergic antagonists increase triglyceride and decrease HDL cholesterol levels. A rise in very-low-density-lipoprotein (VLDL) cholesterol balances the decrease in HDL cholesterol, so that there is no significant change in total cholesterol. α-Adrenergic antagonists decrease triglyceride, increase HDL cholesterol and may decrease VLDL and LDL cholesterol. Labetalol, with both α- and β-adrenergic antagonistic activity, does not affect plasma lipids in a small number of studies. The calcium channel blockers nifedipine and verapamil also have no consistent effect on lipoprotein levels in a small number of studies.

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The metabolic consequences of antihypertensive treatment using diuretics and adrenergic blocking agents are of increasing concern as hypertension is being diagnosed in more young and middle-aged persons and they are placed on lifelong therapy. While this practice is associated with a significant decrease in morbidity and mortality from renal failure, cardiac failure and cerebrovascular accidents,[1] several large prospective studies have failed to show a similar reduction in coronary heart disease in such persons.[2-4] The reason may be multifactorial; there is evidence of increased mortality in diuretic-treated persons with baseline electrocardiographic abnormalities, suggesting an etiologic role for electrolyte abnormalities.[5] In addition, it is becoming increasingly clear that many antihypertensive agents have an adverse effect on another coronary heart disease risk factor—plasma lipids.

Plasma lipids are composed of a number of subfractions, several of which have epidemiologic associations with coronary heart disease. The total cholesterol in a fasting person is the sum of very-low-density-lipoprotein (VLDL) cholesterol, low-density-lipoprotein (LDL) cholesterol and high-density-lipoprotein (HDL) cholesterol. The risk of coronary heart disease is directly proportional to the blood concentrations of LDL cholesterol and inversely proportional to the level of HDL cholesterol.[6] Although plasma triglyceride concentrations may not be directly related to a risk for coronary heart disease, they may serve as a marker for the presence of other risk factors such as other lipoprotein abnormalities, obesity or diabetes.

A substantial number of studies have expored the effects of antihypertensive agents on plasma lipid and lipoprotein levels. Many of these report rather large changes in certain plasma lipids, but because of a small number of subjects the findings have often not been statistically significant. Despite many differences in drug dosage, duration of treatment and laboratory methods, the observations for individual drugs have been surprisingly consistent. In this paper we review and summarize these studies (Figure 1).

The antihypertensive agents that have been best studied fall into four groups: thiazide and loop diuretics, β-adrenergic antagonists, α-adrenergic antagonists and calcium channel blockers. Two drugs do not fit well into these groups: labetalol hydrochloride, which is both a β- and an α-antagonist, and spironolactone, a potassium-sparing diuretic with properties distinct from the thiazide and loop diuretics. These agents are considered separately (Table 4). Because of inconsistent results from study to study, the actual percent changes in each variable were included in the tables even when not

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ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
ISA = intrinsic sympathomimetic activity
LDL = low-density lipoprotein
VLDL = very-low-density lipoprotein

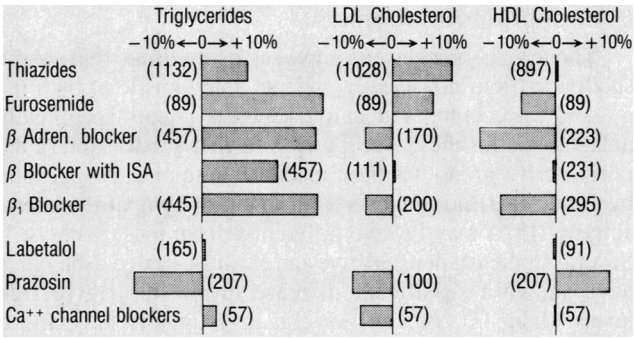

Figure 1.—Summary of data from studies in this review. Each person in each drug group in each manuscript is included (n>2,500). Values accompanying bars represent the number of persons in the stated drug group for which the specified lipoprotein was measured. Because the percent change could not be calculated for data from Lasser et al,[5] data from this study were not included. HDL = high-density-lipoprotein, ISA = intrinsic sympathomimetic activity, LDL = low-density-lipoprotein

statistically significant. This allows readers to make their own conclusions regarding trends of changes in plasma lipid and lipoprotein levels due to individual drugs.

Diuretics

Diuretics include the benzodiathiazide diuretics, the "loop" diuretics and the potassium-sparing diuretics. Benzodiathiazide and related diuretics, more commonly referred to as the thiazide diuretics, are currently the most frequently prescribed antihypertensives.[25] Alterations in lipid metabolism with these agents were first reported by Ames and Hill in 1976, when they found a 25% increase in plasma triglyceride levels in patients taking thiazides and a smaller but significant increase in cholesterol with the use of chlorthalidone.[7] Since this initial report, several authors have confirmed these findings (Table 1). The statistically significant changes include increases in triglyceride and cholesterol values. In addition, those studies reporting statistically insignificant changes reported, with few exceptions, rises in triglyceride and cholesterol levels.

Investigation into the alterations in plasma lipoprotein subfractions has shown that the increase in total cholesterol is associated with an increase in LDL-cholesterol levels. This finding was consistent and reached statistical significance in most studies. Changes in HDL cholesterol have been mixed,

TABLE 1.—*Effects of Thiazide and Loop Diuretic Therapy on Plasma Lipid and Lipoprotein Values**

Reference	Drug	Dose, mg/d	Duration, wk	Patients, Number	Triglycerides	Total Cholesterol	VLDL-C	LDL-C	HDL-C	VLDL-C Plus LDL-C	LDL Determination Method†	Study Design‡
Ames and Hill, 1976[7]	Chlor	Var	Var	32	↑25.7§	↑ 5.2§	...	...	...	...	...	A
Glück et al, 1978[8]	Chlor	100	4	16	↑10.0	↑ 4.0	↑30.0	↑ 8.0§	↓ 5.0	...	D	B
	Chlor	100	6	13	↑10.0	↑ 8.0	↑11.0	↑14.0§	↓12.0§	...	D	A
Glück et al, 1978[8]	Furo	80	4	16	↑16.0	↑ 6.0§	↑ 6.0	↑15.0§	↓ 4.0	...	D	B
	Mefru	50	4	16	↑14.0	↑ 5.0	↑20.0	↑10.0§	↑ 2.0	...	D	B
Ames and Hill, 1978[9]	HCTZ	Var	24	36	↑ 5.6	↑ 6.0§	...	...	...	...	...	A
Helgeland et al, 1978[10]	HCTZ	Var	208	26	↓13.0	↓ 2.4	...	...	↑ 1.4	...	...	A
Rosenthal et al, 1979[11]	Chlor	100	12	21	↑16.0§	↑ 7.8§	↑ 9.0	↑ 9.3§	↓12.0	...	D	A
Van Brummelen et al, 1979[12]	HCTZ	100	36	10	↑ 0.6	↑ 6.5§	...	...	↑ 7.5	...	...	A
Goldman et al, 1980[13]	Chlor	Var	52	508	↑ 7.6§	↑ 5.1§	...	↑10.2§	↑ 0.2	...	I	C
Glück et al, 1980[14]	Chlor	100	6	27	↑ 1.8	↑ 4.3	...	↑20.0§	↓ 3.4	...	D	A
	Chlor	100	6	10	↑ 7.7	↑ 0.9	...	↑ 4.0	↑10.0	...	D	A
Mordasini et al, 1980[15]	Chlor	100	6	12	↑11.0	↑10.6	↓ 5.0	↑15.0§	↓ 5.8	...	D	A
Crisp et al, 1980[16]	Cyclo	0.5	8	13	↑14.0	↑ 3.5	...	↑12.0	↓ 6.7	...	I	B
Leren et al, 1981[17]	HCTZ	50	10	10	↑ 6.1	↑ 2.6	...	...	↑ 2.4	↑2.6	...	B
Grimm et al, 1981[18]	HCTZ	100	6	41	↑17.0§	↑ 6.5§	↑12.5	↑ 5.6	↑ 6.3	...	D	B
	Chlor	100	6	41	↑15.0§	↑ 8.3§	↑ 6.8	↑ 9.5§	↑ 5.5	...	D	B
Weidmann et al, 1981[19]	Indap	2.5	6	18	↓ 8.8	↓ 0.5	...	↓ 1.0	0	...	D	A
Boehringer et al, 1982[20]	Chlor	100	6	22	↑ 4.4	↑ 1.4	↑35.0	↑ 3.0	↑ 2.1	...	D	A
	Chlor	100	6	18	↓ 6.8	↑13.0§	↓20.0	↑21.0§	↑20.0	...	D	A
VA Study, 1982[21]	HCTZ	Var	52	167	↓ 1.8	↓ 1.3	...	...	...	...	...	A
Johnson et al, 1984[22]	Poly	1	4	20	↑14.0§	↑ 4.2§	↑ 8.3	↑ 2.7	↑ 7.5	...	D	A
Lasser et al, 1984[5]	Chlor or HCTZ	100	312	1,021	↑35.0 mg/dl	↑ 4.0 mg/dl	...	↓ 0.7 mg/dl	↓ 0.8 mg/dl	...	I	C
	Chlor or HCTZ	100	312	785	↑37.0 mg/dl	↑ 6.6 mg/dl	...	↑ 1.7 mg/dl	↓ 1.4 mg/dl	...	I	C
Meyer-Sabellek et al, 1984[23]	Indap	2.5	24	12	↑19.0	↑ 5.8	↑31.0	↑ 0.6	↑ 7.5	...	D	A
Bloomgarden et al, 1984[24]	HCTZ	Var	...	89	↑10.0	↑11.0§	...	↑18.0§	0	...	I	E
	Furo	Var	...	57	↑20.0	↑ 2.0	...	↑ 3.0	↓ 6.5	...	I	E

Chlor = chlorthalidone, Cyclo = cyclopenthiazide, Furo = furosemide, HCTZ = hydrochlorothiazide, HDL-C = high-density-lipoprotein cholesterol, Indap = indapamide, LDL-C = low-density-lipoprotein cholesterol, Mefru = mefruside, Poly = polythiazide, Var = variable, VA Study = Veterans Administration Cooperative Study Group, VLDL-C = very-low-density-lipoprotein cholesterol, ↑ = increase, ↓ = decrease

*All lipid values are in percent change unless other units are given.
†D = direct measurement, I = indirect estimation.
‡A = single drug, uncontrolled; B = crossover; C = with a control group; E = cross-sectional.
§$P<.05$.

indicating that HDL-cholesterol levels are probably unaffected by the thiazide diuretics. As would be expected, changes in total plasma triglyceride are reflected in VLDL-cholesterol levels.

Because the duration of treatment in most studies was less than 12 weeks, the long-term effects of the thiazide diuretics on plasma lipids and lipoproteins are less clear. Helgeland and co-workers in 1978 reported an absence of significant change in plasma lipids after four years of hydrochlorothiazide therapy in 26 subjects as part of the Oslo study.[10] A trial by the European Working Party on High Blood Pressure in the Elderly again found no changes in plasma lipids after three years in patients treated with hydrochlorothiazide plus triamterene compared with a control group.[26] The Veterans Administration Cooperative Study Group reported a lack of change in plasma triglyceride or cholesterol levels after one year in 167 persons treated with hydrochlorothiazide. In contrast, other long-term studies document persistent significant increases in plasma triglyceride, cholesterol and LDL cholesterol values. The Veterans Administration-National Heart, Lung and Blood Institute cooperative trial reported a 7.6% increase in triglycerides, a 5.1% increase in cholesterol and a 10.2% increase in LDL-cholesterol levels in 508 patients treated with chlorthalidone for one year, all statistically significant changes.[13] Data from the Multiple Risk Factor Intervention Trial showed a persistent increase in triglyceride and cholesterol levels in both a series of men undergoing usual care and a group of men having special interventions after six years of thiazide treatment; also, there was a small, persistent increase in the LDL-cholesterol value in the men under usual care.[5]

The fact that the results of these long-term clinical trials have been inconclusive may relate to several variables. Simultaneous modifications of diet, exercise and body fat over the course of a study could diminish alterations in plasma lipids caused by the administered drug, making persistent changes in lipid concentrations difficult to show. Several observations support this hypothesis. Two groups of investigators have shown that a lipid-lowering diet can negate the elevation in cholesterol and LDL-cholesterol levels associated with the thiazide diuretics.[5,18] Trends in the American diet towards less saturated fat and cholesterol could have a similar effect. In addition, there is evidence that serum lipid levels tend to fall in normal, older persons as a part of the aging process.[26]

Interestingly, there is some evidence that drug-induced elevations in plasma lipids in women may be limited to the postmenopausal period. Boehringer and associates studied plasma lipid levels in thiazide-treated women and found a statistically significant increase in cholesterol and LDL-cholesterol concentrations only in the postmenopausal group.[20]

Glück and colleagues reported that the loop diuretics furosemide and mefruside cause the same alterations in plasma lipids as the thiazides. A significant increase in plasma LDL-cholesterol concentrations was found with both agents, in the absence of changes in triglyceride and HDL-cholesterol levels.[8]

Effects of the diuretic indapamide on plasma lipids were evaluated in two studies. Neither found significant effects on plasma lipid and lipoprotein values after six weeks of treatment with 2.5 mg per day.[19,23]

A few studies investigating the plasma lipid effects of spironolactone have yielded conflicting results (Table 4). In two, large increases in triglyceride levels were noted with no change in cholesterol values.[9,73] In a third recent study, significant increases in cholesterol and LDL-cholesterol levels occurred with only a small, insignificant increase in triglycerides.[27]

β-Adrenergic Antagonists

The term β-blocker encompasses many drugs that can be subdivided into nonselective agents antagonistic at both the β_1- and β_2-receptor and cardioselective agents specifically antagonistic for the β_1-receptor. A further subdivision of the nonselective group has been made because of the suggestion by Leren that those agents with intrinsic sympathomimetic activity (ISA) may behave differently from those without.[17] Several studies of nonselective and cardioselective β-blockers have shown a significant increase in plasma triglyceride levels (Table 2). In fact, several investigators have found triglyceride increases in excess of 50% of baseline.[33,36,45] Long-term studies indicate that this elevation in triglyceride levels persists beyond the early treatment period. The Veterans Administration Cooperative Study Group found a 25% increase in triglyceride values in 118 patients treated with propranolol hydrochloride for one year.[21] Lehtonen and Viikari reported a 66% increase in triglyceride values after one year of sotalol hydrochloride treatment in 12 patients.[36] Several studies show these changes to last six to eight months during treatment with the cardioselective agents as well.[34,57,60]

While plasma total cholesterol does not appear to be affected by β-adrenergic blockade, changes in the concentrations of individual plasma lipoprotein cholesterols do occur. The most important of these in relation to cardiovascular risk is an impressive reduction in plasma HDL-cholesterol levels found with both nonselective and cardioselective agents. All of the observed statistically significant changes in HDL-cholesterol concentrations have been reductions, and the trend has been a reduction for most of the insignificant changes as well. Lehtonen and co-workers found this reduction in HDL-cholesterol values to persist for at least six months with atenolol[60] and one year with sotalol treatment.[36] Several investigators have found that the decrease in plasma HDL-cholesterol levels with β-adrenergic blockade is balanced by an increase in VLDL-cholesterol levels[34,57,59] and that the combined changes result in a lack of net change in total cholesterol.

Plasma LDL-cholesterol levels have decreased with β-blockade in many studies that have quantified this value, but the change has been statistically significant in only two.[40,44] It is important to note that both studies calculated LDL cholesterol indirectly. Calculated changes in LDL-cholesterol levels may be misleading, as this method assumed VLDL cholesterol to be equivalent to the triglyceride value divided by 5, a relationship that may change with altered lipoprotein metabolism. At this point one might conclude that changes in the LDL-cholesterol value are insignificant.

Dujovne and associates compared the effects of propranolol treatment in patients with normal lipid levels with effects in persons with type II-A and type II-B hyperlipoproteinemia. They found an increase in triglyceride levels in the persons with normal lipid levels, whereas the persons with hyperlipidemia also showed small but statistically significant in-

TABLE 2.—*Effects of β-Adrenergic Antagonists on Plasma Lipid and Lipoprotein Values**

Reference	Drug	Dose, mg/d	Duration, wk	Patients, Number	Triglycerides	Total Cholesterol	VLDL-C	LDL-C	HDL-C	VLDL-C Plus LDL-C	LDL Determination Method†	Study Design‡
Nonselective β-Blocker Without ISA												
Lloyd-Mostyn et al, 1971[28]	Propran	40	2	12	↑30.0	↓ 3.6	...	...	...	...	...	B
Tanaka et al, 1976[29]	Propran	60	8	10	↑ 9.7	↓ 8.6	...	...	...	...	D	A
Brunzell et al, 1977[30]	Propran	Var	...	14	↑72.0§	↑16.0	...	...	...	...	...	C
Shaw et al, 1978[31]	Propran	Var	4	17	↑37.0§	↑ 3.6	...	...	...	...	...	B
Streja and Mymin, 1978[32]	Propran	Var	2	16	↓ 0.4	↓ 5.8	...	↓ 2.6	↓12.0§	...	...	A
Day et al, 1979[33]	Propran	Var	24	16	↑65.0§	↑ 6.0	...	...	...	...	...	A
Bielmann and Leduc, 1979[34]	Propran	160	8	6	↑98.0	...	↑64.0§	↓17.9	↓22.0§	...	D	B
Wright et al, 1979[35]	Propran	160	4	20	↑ 17.0	↓ 1.5	...	...	...	...	...	B
Lehtonen and Viikari, 1979[36]	Sotalol	Var	52	12	↑66.0§	↑16.0§	...	...	↓26.0§	↑32.0§	I	A
Leren et al, 1981[37]	Propran	160	8	23	↑ 23.0§	↓ 1.0	...	...	↓13.0§	↑ 2.1	...	B
Ponti et al, 1983[38]	Propran	160	6	11	↑ 25.0§	↑ 9.1§	...	...	↓ 7.6	...	...	B
Day et al, 1982[39]	Propran	160	12	53	↓51.0§	↓ 1.4	...	↓ 6.1	↓17.0§	...	D	B
Birnbaum et al, 1982[40]	Propran	Var	8	20	↑25.0§	↓ 5.6§	...	↓ 9.0§	↓ 7.0	...	I	B
VA Study, 1982[21]	Propran	Var	52	118	↑25.0§	↑ 3.9§	...	...	...	...	...	A
Goto, 1984[41]	Propran	Var	12	26	↑17.0	↑ 1.0	...	...	↓ 2.0	↑ 2.0	...	A
Lowenstein and Neusy, 1984[42]	Propran	Var	8	29	↑ 0.8	↓ 0.8	...	↑ 0.5	↓ 1.3	...	I	B+D
Johnson et al, 1984[22]	Propran	Var	12	20	↑22.7§	↑ 1.3	↑30.0§	0	↓ 9.6§	...	D	B+D
Dujovone et al, 1984[43]	Propran	Var	12	8	↑37.0§	↑ 1.0	↑44.0	↓ 5.4	↓ 4.3	...	D	B
	Propran	Var	12	9	↑ 5.0	↑ 1.3§	↓ 3.0	↑ 2.3§	↓ 2.2	...	D	B
Murphy et al, 1984[44]	Propran	320	12	9	↑ 7.5	↓ 6.3§	↓ 8.5§	↓ 8.5§	↓ 2.1	...	I	A
With ISA												
England et al, 1978[45]	Pindolol	Var	4	17	↑28.0§	↑ 5.4	...	...	...	...	...	B+D
Leren et al, 1981[17]	Pindolol	Var	10	10	↓ 9.0	↓ 4.6	...	...	↑ 3.9	↓ 6.6	...	A
Pasotti et al, 1982[46]	Pindolol	Var	12	16	↑ 1.8	↑ 0.3	...	↓ 3.6	↑20.0§	...	I	B
Lehtonen et al, 1982[47]	Pindolol	Var	24	20	↑ 0.9	↓ 4.3§	...	...	↑ 3.5	...	...	A
Karmakoski et al, 1983[48]	Pindolol	Var	16	13	↓17.0	↑ 1.5	...	↑18.0	↑12.0	...	D	C
Murphy et al, 1984[44]	Pindolol	20	12	8	↓ 6.8	↓ 8.9	...	↓10.8	↓ 4.6	...	I	A
Lloyd-Mostyn et al, 1971[28]	Oxpren	40	2	10	↑ 3.3	↑ 0.3	...	...	...	...	...	B
Sommers et al, 1981[49]	Oxpren	120	3	80	↑ 6.8	↓12.7§	...	...	0	...	...	B
Ballantyne et al, 1981[50]	Oxpren	160	16	9	↑13.0	↑ 7.0	↓ 3.0	↑11.0	↑ 1.4	...	D	A
Kjeldsen et al, 1982[51]	Oxpren	160	18	10	↑20.0	↑ 1.2	...	...	↓11.4§	↑ 4.1	...	A
Day et al, 1982[39]	Oxpren	160	12	53	↑26.0§	↓ 0.3	...	↓ 3.9	↓11.5§	...	D	B
Simons et al, 1982[52]	Oxpren	Var	32	12	↑33.0§	↑ 7.0	↑50.0	↑ 7.3	↑11.5	...	D	A
β_1-Blockers												
Lloyd-Mostyn et al, 1971[28]	Pract	200	2	12	↑ 7.5	↓ 2.0	...	...	...	...	...	B
Waal-Manning, 1976[53]	Metop	...	12	14	↑34.0§	↓ 2.5	...	...	...	...	...	A
Nilsson et al, 1977[54]	Metop	Var	12	9	↓10.0	...	...	...	...	...	...	A
England et al, 1978[45]	Atenolol	100	4	17	↑62.0§	↑ 2.1	...	...	...	...	...	B+D
	Metop	100	4	17	↑32.0§	↑ 2.0	...	...	...	...	...	B+D
Day et al, 1979[33]	Atenolol	Var	24	14	↑24.0§	↑ 1.6	...	...	...	...	...	A
Bielmann and Leduc, 1979[34]	Metop	200	8	6	↑40.0	...	↓ 4.8	↓ 8.6	↑ 6.1	...	D	B
Wright et al, 1979[35]	Metop	200	4	20	↑13.2	↑ 0.9	...	...	...	...	...	B
Beinart et al, 1979[55]	Metop	200	12	12	0	↑ 8.6	...	...	...	...	...	A
England et al, 1980[56]	Metop	Var	12	34	↑10.0§	↓ 1.0	...	...	↓13.0§	...	...	B
	Atenolol	100	12	34	↑ 6.0§	↓ 0.8	...	...	↓10.0	...	...	B
Eliasson et al, 1981[57]	Atenolol	100	32	15	↑26.0§	↑ 7.4	↑29.0§	↑ 3.7	↓ 1.6	...	D	A
Thulin et al, 1981[58]	Atenolol	Var	6	33	↑27.0§	↓ 1.7	...	...	...	...	...	B
Kjeldsen et al, 1982[51]	Atenolol	100	18	9	↑17.9§	↓ 1.6	...	...	↓16.5	↑ 2.6	...	A
Day et al, 1982[39]	Atenolol	100	12	53	↑24.0§	↑ 3.1	...	↓ 5.2	↓ 7.0§	...	D	B
	Metop	200	12	53	↑14.0§	↓ 1.4	...	↓ 4.4	↓13.0§	...	D	B
Birnbaum et al, 1982[40]	Acebut	Var	8	17	↓ 2.1	↓ 7.4	...	↓12.0§	↓ 2.4	...	I	B
Pasotti et al, 1982[46]	Metop	Var	12	16	↑ 0.5	↑ 3.1	...	↑ 4.7	↑ 0.7	...	I	B
Rössner and Weiner, 1983[59]	Atenolol	50	12	20	↑ 6.4	↓ 2.8	↑ 4.0	↓ 1.5	↓ 2.1	...	D	B
	Metop	200	12	20	↓ 4.0	↑ 2.5	↑29.0§	↓ 3.2	↓ 7.7§	...	D	B
Lehtonen and Marniemi, 1984[60]	Atenolol	100	24	18	↑37.0§	8.0§	...	...	↓11.8§	...	...	A

Acebut = acebutolol, HDL-C = high-density-lipoprotein cholesterol, ISA = intrinsic sympathomimetic activity, LDL-C = low-density-lipoprotein cholesterol, Metop = metoprolol, Oxpren = oxprenolol hydrochloride, Pract = practolol, Propran = propranolol hydrochloride, Var = variable, VA Study = Veterans Administration Cooperative Study Group, VLDL-C = very-low-density-lipoprotein cholesterol, ↑ = increase, ↓ = decrease

*All lipid values are in percent change unless other units are given.
†D = direct measurement, I = indirect estimation.
‡A = single drug, uncontrolled; B = crossover; C = with a control group; D = studied drug added as a second drug, first drug listed in footnote.
§$P < .05$.

creases in total cholesterol and LDL-cholesterol levels with no change in triglycerides.[43]

Leren and colleagues reported in 1981 that pindolol, a nonselective β-blocker, did not appear to affect triglyceride or lipoprotein levels and speculated that this might be due to the high intrinsic sympathomimetic activity of the drug.[17] Unlike other β-blockers, pindolol may cause the HDL-cholesterol level to rise, with increases as high as 20% reported.[46] England and co-workers found a 28% increase in triglycerides when pindolol was added to a regimen with chlorothiazide,[45] but either no change or statistically nonsignificant decreases in triglyceride levels have been reported in other studies.

Oxprenolol hydrochloride is another nonselective β-blocker that possesses ISA. Two studies have found statistically significant decreases in plasma HDL-cholesterol values of about 11%.[39,51] Day and colleagues found triglyceride levels to be elevated significantly with the use of oxprenolol[39]; other studies showed a trend for triglyceride levels to increase. Thus, the effects on plasma lipid and lipoprotein values associated with oxprenolol treatment are more similar to those noted with β-blockers without ISA than to those occurring with the use of pindolol. This is probably related to the relative ISA potency of the two drugs, with pindolol having greater partial β-agonist activity than oxprenolol.[62]

α-Adrenergic Antagonist

Prazosin hydrochloride, an α_1-antagonist, has stirred considerable interest since Leren and associates reported in 1981 that this drug may have a beneficial effect on plasma lipids and lipoprotein levels. In a crossover trial of propranolol in seven subjects, Leren and co-workers found prazosin therapy to significantly reduce triglycerides, total cholesterol and the sum of VLDL cholesterol plus LDL cholesterol, with no change in HDL-cholesterol levels.[37] Since this report, a number of studies have been conducted investigating plasma lipid and lipoprotein changes with prazosin therapy (Table 3). In many studies designed with prazosin added to a previous drug regimen, the results have been quite consistent and include a reduction in triglyceride and an increase in HDL-cholesterol levels. There has been a trend of a decrease in cholesterol, but the change has not been large. A few studies investigating changes in VLDL- and LDL-cholesterol levels have found decreases in both of these lipoproteins, with two groups reporting statistically significant reductions. Rouffy and Jaillard reported that the mean LDL-cholesterol level decreased 13% and VLDL cholesterol 18%.[71] Lowenstein and Neusy reported a 9.4% reduction in LDL-cholesterol concentrations with prazosin therapy.[42] In conclusion, prazosin tends to lower triglyceride, raise HDL cholesterol and may also lower LDL- and VLDL-cholesterol concentrations.

Two studies have focused on the plasma lipid changes with prazosin therapy given for one year. Lithell and associates failed to observe significant changes in plasma lipids after one year,[68] whereas Takabatake and associates reported a persistent increase in HDL-cholesterol levels after the same period.[72]

α- and β-Adrenergic Antagonists

Labetalol is a nonselective β-blocker that also has α-antagonistic activity. This drug recently was released for use in the United States. Five studies have evaluated changes in triglyceride levels with labetalol hydrochloride therapy, with four reporting nonsignificant increases (Table 4).[39,49,58,74] Changes in plasma HDL-cholesterol values were assessed in only two studies, with one reporting no change and the other a nonsignificant decrease.[39,49] Sommers and colleagues reported no change in HDL-cholesterol levels but found a statistically significant decrease in total cholesterol of 14%.[49] No studies have investigated changes in LDL- or VLDL-cholesterol values with the use of labetalol.

Calcium Channel Blockers

Calcium channel blockers are relatively new agents that are rapidly becoming popular in the treatment of angina and hypertension. Nifedipine and verapamil, two members of this

TABLE 3.—*Effects of α-Antagonist (Prazosin Hydrochloride) Therapy on Plasma Lipid and Lipoprotein Values**

Reference	Dose, mg/d	Duration, wk	Patients, Number	Triglycerides	Total Cholesterol	VLDL-C	LDL-C	HDL-C	VLDL-C Plus LDL-C	LDL Determination Method†	Study Design‡
Kirkendall et al, 1978[63]	Var	8	13	...	↓ 5.3§	...	...	...	...	...	A
Leren et al, 1980[37]	4	8	7	↓16.5§	↓ 9.0§	...	...	↓ 4.0	↓10.0§	...	B
Leichter and Baumgardner, 1981[64]	Var	Var	7	↑ 4.0	↓ 4.3	...	...	↑ 6.0	...	...	A+D
Velasco et al, 1982[65]	Var	12	19	↓27.0	↑ 7.5	↓22.0	↓ 2.2	↑19.6	...	D	A+D
Kokubu et al, 1982[66]	Var	12	14	↑ 0.9	↓ 0.7	...	...	↑12.5	↓ 4.5	...	A
Havard et al, 1982[67]	Var	8	17	↓14.0	↓ 0.9	...	...	↑ 7.7	...	...	A
Lithell et al, 1982[68]	Var	52	8	↓ 0.7	↓ 3.2	↓15.0	↓ 6.5	0	...	D	A
Goto, 1984[41]	Var	12	17	↓21.0§	↓ 1.1	...	...	↓ 4.0	↓ 4.2	...	A+D
Lowenstein and Neusy, 1984[42]	Var	8	29	↓20.0§	↓ 7.3§	...	↓ 9.4§	↑ 6.0§	...	I	A+D
Kather and Sauberlich, 1984[69]	Var	12	15	↑ 6.8	↑ 2.8	...	...	↑ 8.5§	...	...	A
Mauersberger, 1984[70]	Var	8	15	↓ 3.2	↓ 2.3	...	...	↑10.9§	...	...	A+D
Rouffy and Jaillard, 1984[71]	Var	13	24	↓ 9.8§	↓ 7.9§	↓19.0§	↓13.0§	↑13.0§	...	D	A
Johnson et al, 1984[22]	Var	12	20	↓ 5.7	↑ 2.3	↓12.0	↑ 4.7	↑ 3.9	...	D	B+D
Takabatake et al, 1984[72]	Var	52	15	↓ 7.3	↑ 2.0	...	...	↑17.0§	...	...	A

HDL-C = high-density-lipoprotein cholesterol, LDL-C = low-density-lipoprotein cholesterol, Var = variable, VLDL-C = very-low-density-lipoprotein cholesterol, ↑ = increase, ↓ = decrease

*All lipid values are in percent change unless other units are given.
†D = direct measurement, I = indirect estimation.
‡A = single drug, uncontrolled; B = crossover; D = studied drug added as a second drug.
§$P < .05$.

class, have been investigated for their effects on plasma lipids (Table 4). Vessby and co-workers reported in 1983 that nifedipine failed to significantly alter plasma lipid and lipoprotein values in 11 subjects.[79] In a study of verapamil in 12 patients, 10 with angina, Walldius found statistically significant decreases in both total and LDL-cholesterol concentrations.[76] Two other investigators failed to verify this, although they did find insignificant decreases in LDL-cholesterol levels.[77,78]

Diabetes Mellitus and Antihypertensive Therapy

In several studies persons with diabetes mellitus had alterations in plasma lipids similar to those without diabetes when treated with various antihypertensive drugs. Bloomgarden and associates found a significantly higher level of LDL cholesterol in a cross-sectional study of patients with diabetes treated with thiazides compared with diabetic patients not receiving drugs.[24] Other studies of patients with diabetes found nonsignificant elevations in triglyceride levels when treated with propranolol or metoprolol[35] and a nonsignificant elevation in HDL-cholesterol concentrations when treated with prazosin.[64]

Pronounced hypertriglyceridemia (a triglyceride level of greater than 2,000 mg per dl as chylomicrons and VLDL) has been reported in persons with diabetes treated with β-adrenergic blocking agents or diuretics.[80] These patients are unique in that they have inherited both a familial form of hypertriglyceridemia and the propensity for diabetes mellitus. The simultaneous inheritance of these two independent disorders appears to make them particularly sensitive to these agents.[81]

HDL-Cholesterol Subfractions

There is evidence that the HDL-cholesterol subfraction HDL_2 may be a better predictor of coronary artery disease than HDL cholesterol.[83] In several recent studies the effects of antihypertensive drugs on HDL-cholesterol subfractions were investigated (Table 5). Lehtonen and Marniemi and Meltzer and associates found that the decreases in HDL-cholesterol levels seen with the use of β-blockers were primarily due to decreases in HDL_2, without a significant change in the HDL_3 subfraction.[60,82] Rouffy and Jaillard also found a decrease in HDL-cholesterol levels with atenolol therapy to be associated with a decrease in HDL_2.[71] In single studies, the use of the drugs prazosin and verapamil have been associated with increases in the HDL_3 subfraction.[76,82]

Apoproteins

In addition to the individual lipoproteins discussed previously, apoproteins have a predictive value for coronary artery disease. Specifically, persons with coronary artery disease have had elevated levels of apoprotein B compared with controls matched for total cholesterol and triglyceride levels.[84] The ratio of apoprotein A-I to apoprotein A-II, both of which are found in HDL cholesterol, can be used as a rough guide to changes in HDL_2 levels. An increase in this ratio is associated with an elevation in HDL_2.[85] Changes in specific apoprotein levels with antihypertensive medications have been evaluated by several investigators (Table 6).

The thiazide diuretics significantly altered apoprotein levels in only one study. Boehringer and colleagues found a 16% increase in apoprotein B levels in postmenopausal women treated with chlorthalidone.[20] Other studies show a trend towards an increase in apoprotein B that parallels the increase in LDL-cholesterol values. Changes in apoproteins A-I and A-II have been nonsignificant.

β-Blockade has been found to decrease apoprotein A-I in a study by Rouffy and Jaillard and to decrease apoprotein A-I plus A-II levels in a study by England and co-workers.[56,71] This result is in agreement with the previously mentioned decreases in HDL cholesterol. Although Rouffy and Jaillard have found a significant increase in apoprotein B values with

TABLE 4.—*Effects of Spironolactone, Labetalol and Calcium Channel Blocker Therapy on Plasma Lipid and Lipoprotein Values**

Reference	Dose, mg/d	Duration, wk	Patients, Number	Triglycerides	Total Cholesterol	VLDL-C	LDL-C	HDL-C	VLDL-C Plus LDL-C	LDL Determination Method†	Study Design‡
Spironolactone											
Ames and Hill, 1978[9]	Var	24	20	↑19.0§	↑ 2.2	...	...	...	...	...	A
Schersten et al, 1980[73]	200	8	45	↑13.0§	↑ 1.6	...	...	...	...	...	A
Hunninghake et al, 1984[27]	100	6	...	↑ 5.8	↑ 3.6§	...	↑ 5.3§	↓ 1.5	...	...	B
Labetalol											
Pagnun et al, 1979[74]	Var	16	8	↑27.0	↓ 1.6	...	...	...	...	...	A
McGonigle et al, 1981[75]	...	52	33	↓12.0	↓ 4.0	...	...	...	...	...	A
Sommers et al, 1981[49]	300	3	80	↑ 2.0	↓14.0§	...	...	0	...	...	B
Thulin et al, 1981[58]	Var	6	33	↑ 6.7	↑ 3.3	...	...	...	...	...	B
Day et al, 1982[39]	400	6	11	↑ 1.2	↑ 6.6	...	...	↓ 7.4	...	...	B
Calcium Channel Blockers—Verapamil											
Walldius, 1982[76]	Var	24	12	↓ 8.1	↓ 7.6§	↓15.0	↓ 8.5§	↓ 0.7	...	D	A
Faergeman et al, 1982[77]	360	24	13	↑ 9.0	↓ 5.5	↑66.0	↓12.0	↓ 8.0	...	D	C
Strunge et al, 1982[78]	...	24	21	↓ 1.3	↑ 6.7	...	↓ 1.7	↓ 1.0	...	I	C
Nifedipine											
Vessby et al, 1983[79]	80	12	11	↑13.0	...	↓11.0	↓ 0.2	↑ 9.5	...	D	A

HDL-C = high-density-lipoprotein cholesterol, LDL-C = low-density-lipoprotein cholesterol, Var = variable, VLDL-C = very-low-density-lipoprotein cholesterol, ↑ = increase, ↓ = decrease

*All lipid values are in percent change unless other units are given.
†D = direct measurement, I = indirect estimation.
‡A = single drug, uncontrolled; B = crossover; C = with a control group.
§$P < .05$.

TABLE 5.—*Drug Therapy and High-Density-Lipoprotein Cholesterol (HDL-C) Subfractions**

Reference	Drug	HDL-C	HDL_2	HDL_3
Murphy et al, 1984[44]	Propranolol hydrochloride	↓ 2.1	↓16.0	↑ 5.9
	Pindolol	↓ 4.6	↓ 6.1	↓ 3.8
Lehtonen and Marniemi, 1984[60]	Atenolol	↓12.0†	↓28.0†	↓ 3.8
Rouffy and Jaillard, 1984[71]	Atenolol	↓10.0†	↓ 6.1†	. . .
Waldius, 1982[76]	Verapamil	↓ 0.7	↓ 8.7	↑12.0†
Meltzer et al, 1984[82]	Propranolol	↓21.0†	↓23.0†	↓15.0
	Prazosin hydrochloride	↑ 9.9	↓ 6.7	↑26.0†

↑ = increase, ↓ = decrease

*Values represent percent change.
†$P \leq .05$.

TABLE 6.—*Effects of Adrenergic-Blocking Agents on Apoproteins**

Reference	Drug	Apoproteins B	Apoproteins A-I	Apoproteins A-II
Glück et al, 1980[14]	Chlorthalidone	↑ 2.8	0	↓2.6
	Chlorthalidone	↑ 5.3	↓ 0.8	↑1.9
Mordasini et al, 1980[15]	Chlorthalidone	↑ 9.8	↓ 1.7	↓7.5
Weidmann et al, 1981[19]	Indapamide	↓ 2.7	. . .	. . .
Boehringer et al, 1982[20]	Chlorthalidone	0	↓ 4.8	↓2.3
	Chlorthalidone	↑16.0†	↓ 4.7	↓7.8
England et al, 1980[56]	Metoprolol	↓ 2.3	↓ 9.1† (A-I plus A-II)	
	Atenolol	↓13.0	↓ 9.8† (A-I plus A-II)	
Lithell et al, 1982[68]	Prazosin hydrochloride	↓ 2.5	↑ 1.9	↓3.1
Rouffy and Jaillard, 1984[71]	Atenolol	↑ 2.9†	↓ 6.4†	. . .
	Prazosin	↓ 7.3†	↑11.0†	. . .

↑ = increase, ↓ = decrease

*Values represent percent change.
†$P \leq .05$.

atenolol therapy,[71] significant changes in this apoprotein have not been found by other authors. α-Blockade with the use of prazosin was found by Rouffy and Jaillard to cause a decrease in apoprotein B and an increase in apoprotein A-I levels.[71] Lithell and associates found no significant changes in the apoproteins with prazosin, however.[68]

Discussion

From the above observations, it is possible to make some general mechanistic speculations as to how the described drugs cause their characteristic changes in lipid and lipoprotein concentrations. β-Blockade appears to increase plasma triglyceride and decrease HDL-cholesterol levels, whereas α-blockade seems to cause a decrease in triglyceride and an increase in HDL-cholesterol levels. These findings support a theory first described by Day and colleagues that unopposed α-stimulation may be responsible for the decrease in HDL cholesterol and an increase in triglyceride levels seen with β-blocker treatment.[39] Day and co-workers proposed that unopposed α-stimulation causes these changes through the inhibition of lipoprotein lipase.[39] There is no direct evidence that this occurs, however. Attempts to infer that a decreased Intralipid (an emulsion of soybean triglyceride and phospholipid) clearance[39] associated with β-blocker therapy represents adrenergic inhibition of lipoprotein lipase[86] may be misleading. The lipoprotein lipase triglyceride removal system is a saturable enzyme system in humans.[87] The delayed clearance of Intralipid may reflect an increase in serum triglyceride levels due to an increased input of very-low-density lipoprotein; a relative defect in clearance may be due to the increase in input.

Hooper and associates in 1981 reported a 10% increase in plasma HDL cholesterol with the use of terbutaline, an adrenergic agonist relatively selective for the β_2-receptor.[88] This evidence, plus reports of antagonistic effects of α- and β-activity on human adipocyte activity,[69,89] led to the proposal that changes in triglyceride and HDL-cholesterol levels are related to the ratio of total α- and β-activity, with an increase in the ratio (as with β-blockade) leading to increased triglyceride and decreased HDL-cholesterol levels; a decrease in the ratio (as with α-blockade) leads to decreased triglyceride and increased HDL-cholesterol values. Labetalol, with both α- and β-adrenergic antagonistic activity, would not be expected to greatly alter this adrenergic ratio. Similarly, pindolol, a partial agonist of the β-receptor, acts as both a β-adrenergic agonist and antagonist and would not greatly alter this adrenergic ratio.

It is possible to relate the thiazide- and loop diuretic-induced elevations in triglyceride levels to the above scheme. These agents, through a depletion of intravascular volume, cause a reactive elevation in plasma catecholamine levels with an increase in α-adrenergic activity. There does not appear to be a concomitant decrease in HDL-cholesterol concentrations, however, as would be predicted by the above hypothesis. Further, the mechanism for the increase in LDL cholesterol seen with these agents is obscure.

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