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β-Blocker Effects on Plasma Lipids in Antihypertensive Therapy: Importance of the Duration of Treatment and the Lipid Status Before Treatment

Roberto Fogari, Annalisa Zoppi, Franco Tettamanti, Luigi Poletti, Pierangelo Lazzari, *Carlo Pasotti, and †Luca Corradi

*Department of Internal Medicine and Therapeutics, IRCCS Policlinico S. Matteo, University of Pavia; *Hypertension Center, Voghera Hospital; and †Hypertension Center, Broni-Stradella Hospital, Pavia, Italy*

Summary: The aim of this study was to evaluate the effects of long-term monotherapy with four β-blockers provided with different pharmacological properties on plasma lipids in both normocholesterolemic and hypercholesterolemic hypertensive patients. After a 1-month run-in period on placebo, 70 hypertensive patients with basal total cholesterol (TC) ≤ 220 mg/dl were treated for 3 years with propranolol 160 mg/day or atenolol 100 mg/day or bisoprolol 10 mg/day or mepindolol 10 mg/day, while 59 hypertensive patients with basal TC > 220 mg/dl were given the same β-blockers at the same dosage for 6 months. In both normocholesterolemic and hypercholesterolemic hypertensive patients, HDL-C and triglyceride (TG) levels showed significant changes that appeared to be related to the type of β-blocker used and to the duration of therapy. Nonselective, non-ISA (intrinsic sympathomimetic activity) propranolol caused the most pronounced changes, decreasing HDL-C and increasing TG concentrations; β_1-selective atenolol and bisoprolol had similar, but less remarkable effects; even more discrete changes were observed on mepindolol (with ISA). The variations in HDL-C and TG values reached their peak in 6–12 months of β-blocker therapy; then, after a plateau phase, they showed a progressive trend toward pretreatment levels. In hypercholesterolemic patients, the percent change in both HDL-C and TG values was lower compared to normocholesterolemic patients. **Key Words:** Hypertension—β-Blockers—Lipids.

Over the past few years, accumulating evidence demonstrated that several of the drugs used for standard antihypertensive therapy may have detrimental long-term effects on the lipid profile (1–3). The clinical significance of these drug-induced changes in lipid metabolism has not yet been fully elucidated; however, it has been suggested that such changes may be partly responsible for the relative lack of efficacy of antihypertensive treatment in reducing the incidence of coronary artery disease (CAD) and should be taken into account when evaluating the risk/benefit ratio of antihypertensive therapy (4–8).

Treatment with β-blocking drugs has been associated with an increase in plasma triglyceride (TG) and a fall in high-density lipoprotein (HDL)-cholesterol levels (9–11). These changes, particularly a decreased HDL-C/LDL-C ratio, have been assumed to increase the risk of coronary atherosclerosis (12,13), which may offset the antihypertensive benefits of β-blockers and reduce their potential for primary cardioprotection. However, the relevance of the duration of β-blocker therapy has not been established: in only 20% of the reports in literature that detailed the effects of different β-blockers on plasma lipids was the β-blocker given for more than 1 year, and in only 40% was the β-blocker administered as monotherapy with a duration of treatment greater than 1 month. The pretreatment level of plasma lipids theoretically could also have an influence; little is known about this point. Moreover, different types of β-blockers may vary in their quantitative and qualitative effects on lipoprotein metabolism depending on their individual pharmacological properties: nonselective, nonintrinsic sympathomimetic activity (ISA) β-blockers have been reported to increase TG and decrease HDL-C plasma levels to a greater extent than β-selective ones (14–17), whereas β-blockers with ISA have even more discrete effects on TG and elevate HDL-C values (18–20).

This study was undertaken to evaluate the possible

Address correspondence and reprint requests to Prof. Roberto Fogari at Clinica Medica I, Policlinico S. Matteo, Piazza Golgi 6, 27100 Pavia, Italy.

time-related effects of long-term monotherapy with four β-blockers provided with different pharmacological properties on plasma lipids in both normocholesterolemic and hypercholesterolemic hypertensive patients.

METHODS

One hundred twenty-nine mild essential hypertensives, all males, were studied. Group I included 70 patients, aged 35–56 years (mean age: 46.5 years) with plasma total cholesterol (TC) ≤ 220 mg/dl; group II was composed of 59 patients, aged 39–63 years (mean age: 51.3 years), with plasma TC > 220 mg/dl. All patients worked in the same community in which there was an established work-site hypertension treatment program. Exclusion criteria were second- and third-degree atrioventricular (AV) heart block, heart failure, pronounced bradycardia, bronchial asthma, and severe renal or hepatic impairment. All patients gave their informed consent.

After a 1-month washout phase followed by a 1-month placebo period, patients in group I were randomly assigned to receive propranolol 160 mg/day (n = 15), atenolol 100 mg/day (n = 22), bisoprolol 10 mg/day (n = 17), or mepindolol 10 mg/day (n = 16). They were followed for 3 years. The patients in group II were stratified on the basis of their plasma TC and then randomly assigned to β-blocker treatment (propranolol, n = 14; atenolol, n = 16; bisoprolol, n = 15; mepindolol, n = 14) at the same doses as in group I. They were followed for 6 months. No special diet was prescribed but patients in group II were invited to limit saturated fat and cholesterol intake.

In both groups, patients were checked before and after the placebo period and every 6 months from the beginning of the active treatment. At each visit, systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) were measured. Fasting venous plasma samples were drawn for evaluation of TC, HDL-C, and TG. TC and TG were determined by the enzymatic method of the Chemetron Company. HDL-C was measured by the enzymatic method of Roschlau (21), after LDL and VLDL precipitation with polyethylene glycol by the method of Viikari (22).

The results are expressed as the mean ± SD. Statistical significance was evaluated by analysis of variance and by the Tuckey test for multiple observations. Significance was defined as $p < 0.05$.

RESULTS

The mean values of TC, HDL-C and TG at various time intervals after the start of treatment with the different β-blockers in the patients with basal TC ≤ 220 mg/dl are shown in Table 1. There was a slight, not significant increase in TC levels after 6 months of treatment with all of the β-blockers in the study. Thereafter, a slight decrease or no change in TC values were observed until the end of the second year of treatment, when TC levels showed a mild but distinct decrease on all β-blockers. At the 3-year examination, such decreases in TC values ranged from 5 mg/dl in the atenolol-treated group to 10 mg/dl in the mepindolol group. However, no final value of TC level in any group was statistically different compared to the pretreatment values.

TABLE 1. *Mean values (±SD) of total cholesterol (TC), HDL-cholesterol (HDL-C), and triglycerides (TG) at various time intervals from the start of treatment with propranolol, atenolol, bisoprolol, and mepindolol in normocholesterolemic patients*

Drug	Months of treatment	TC (mg/dl)	HDL-C (mg/dl)	TG (mg/dl)
Propranolol (n = 15)	0	200 ± 24	55 ± 8	112 ± 41
	6	205 ± 25	43 ± 7[b]	156 ± 41[b]
	12	205 ± 29	37 ± 9[b]	153 ± 41[b]
	24	197 ± 28	39 ± 8[b]	150 ± 41[b]
	36	194 ± 26	50 ± 9	124 ± 40
Atenolol (n = 22)	0	202 ± 26	54 ± 8	112 ± 39
	6	207 ± 28	46 ± 7[b]	141 ± 44[b]
	12	202 ± 30	45 ± 9[b]	140 ± 42[b]
	24	200 ± 31	43 ± 7[b]	142 ± 44[b]
	36	197 ± 29	46 ± 8[a]	129 ± 24[a]
Bisoprolol (n = 17)	0	201 ± 24	56 ± 8	110 ± 33
	6	204 ± 26	52 ± 8	135 ± 40[b]
	12	202 ± 27	56 ± 8	134 ± 40[b]
	24	200 ± 28	57 ± 8	133 ± 38[b]
	36	195 ± 27	56 ± 9	120 ± 34
Mepindolol (n = 16)	0	200 ± 25	55 ± 9	112 ± 24
	6	201 ± 24	56 ± 10	134 ± 28[a]
	12	198 ± 26	59 ± 9	128 ± 25
	24	195 ± 26	58 ± 9	124 ± 27
	36	192 ± 26	57 ± 9	120 ± 25

[a] $p < 0.05$ vs. baseline.
[b] $p < 0.01$ vs. baseline.

In our study, bisoprolol and mepindolol did not significantly affect HDL-C levels, which were substantially unchanged during any of the treatment periods with both β-blockers (Fig. 1). On the contrary, both propranolol and atenolol significantly reduced HDL-C concentrations. Such an effect was more pronounced on propranolol and reached its peak after 1 year of treatment. After this peak phase, a small stepwise increase in plasma HDL-C levels was observed in the atenolol-treated patients from the second year of treatment onwards; in the propranolol-treated group, HDL-C changes paralleled those observed on atenolol until the 2-year examination; thereafter, a distinct, quicker increase was detected so that, at the 3-year examination, HDL-C values on propranolol, although lower than pretreatment values, were significantly higher than peak values.

As depicted in Fig. 2, significant increases in TG concentrations were observed with all four β-blockers after 6 months of treatment. Such a rise in TG levels was greater in patients on propranolol (+37%) and progressively less pronounced on atenolol (+26%), bisoprolol (+23%), and mepindolol (+19%). After this peak, different behaviors were seen: In the propranolol- and mepindolol-treated patients, TG levels began immediately to decrease throughout the study. In the bisoprolol and atenolol groups, TG concentrations showed a plateau phase until the end of the second year; afterwards, they began to decrease. Such a decrease was parallel in these two groups for 12 months up to the end of treatment. At the 3-year final

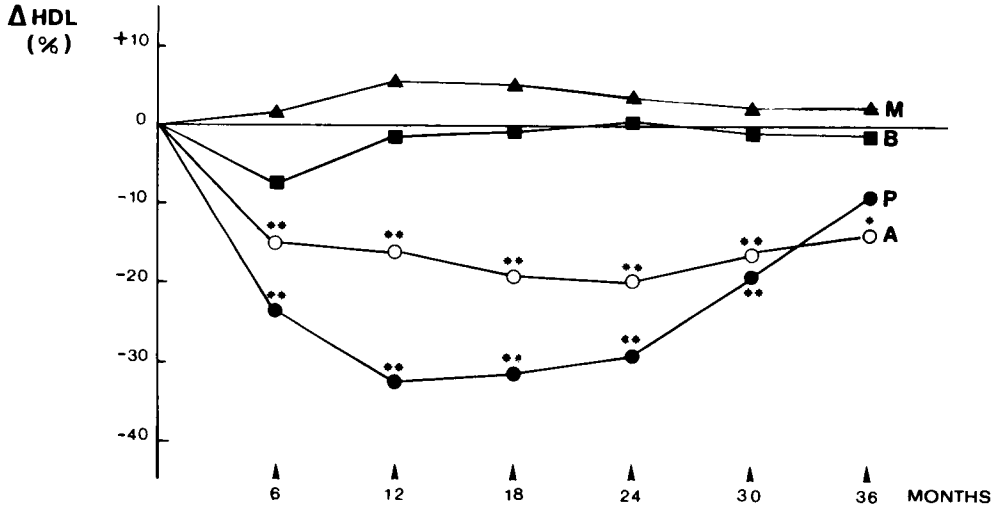

FIG. 1. Percentage changes in plasma HDL-C in normocholesterolemic hypertensive patients during long-term treatment with four different β-blockers (P = propranolol, A = atenolol, B = bisoprolol, M = mepindolol). $^{*}p < 0.05$, $^{**}p < 0.01$ vs. baseline.

examination, the TG levels were no longer significantly elevated with propranolol, bisoprolol, and mepindolol whereas on atenolol a small but significant ($p < 0.05$) increase was still detectable (see also Table 1).

The β-blocker–induced changes in TC, HDL-C, and TG mean values in hypertensive patients with basal TC > 220 mg/dl are shown in Table 2. In all four treatment groups, there was a trend toward lower TC values after 6 months of therapy. This was in contrast with that observed in the normal lipid patients, which showed a mild trend upwards or no change in TC values after 6 months of treatment with any β-blocker.

The effects of the four β-blockers in the study on HDL-C and TG plasma concentrations were qualitatively similar to those observed in the normocholesterolemic hypertensive patients (increase in TG and decrease in HDL-C). Again, treatment with β-selective (atenolol, bisoprolol) and ISA-provided β-blockers (mepindolol) was associated with less pronounced alterations in HDL-C and TG levels compared to those induced by the nonselective, non-ISA propranolol. The HDL-C decrease and the increase in TG levels were statistically significant with propranolol and atenolol, whereas the changes induced by bisoprolol and mepindolol did not reach statistical significance. Figures 3 and 4 show the comparison of TG and HDL-C percentage changes at the 6-month examination between the two groups of patients: normocholesterolemic and hypercholesterolemic ones. The percentage changes in both TG and HDL-C values were smaller in patients with plasma cholesterol > 220 mg/dl. For both groups, the

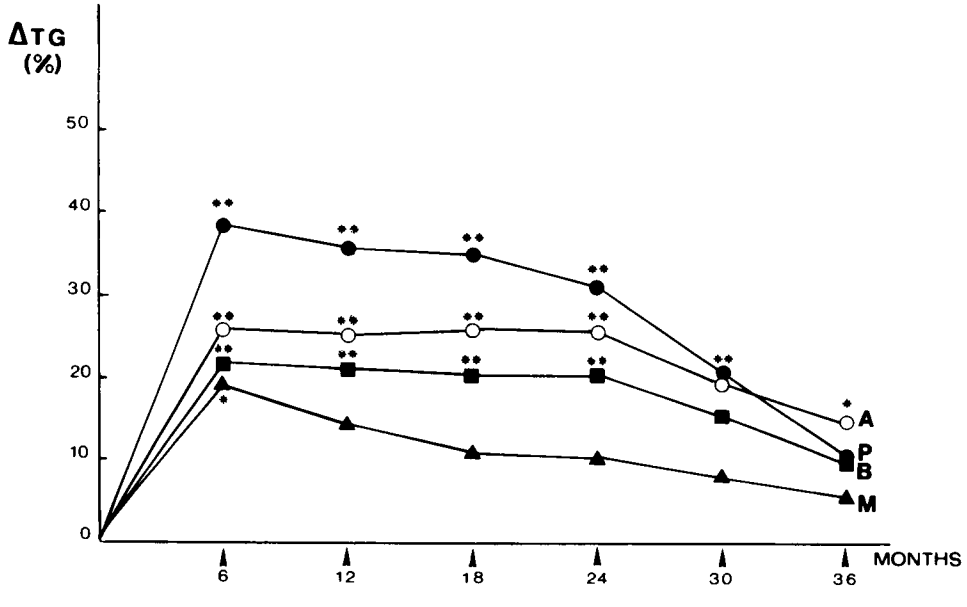

FIG. 2. Percentage changes in plasma TG in normocholesterolemic hypertensive patients during long-term treatment with four different β-blockers (P = propranolol, A = atenolol, B = bisoprolol, M = mepindolol). $^{*}p < 0.05$, $^{**}p < 0.01$ vs. baseline.

TABLE 2. *Mean values (±SD) of total cholesterol (TC), HDL-cholesterol (HDL-C), and triglycerides (TG) before and after 6 months of treatment with propranolol, atenolol, bisoprolol, and mepindolol in hypercholesterolemic patients*

Drug	Months of treatment	TC (mg/dl)	HDL-C (md/dl)	TG (mg/dl)
Propranolol	0	282 ± 29	45 ± 10	165 ± 67
(n = 14)	6	277 ± 30	36 ± 10[a]	203 ± 68[a]
Atenolol	0	279 ± 32	44 ± 11	178 ± 68
(n = 16)	6	276 ± 33	37 ± 11[a]	213 ± 66[a]
Bisoprolol	0	280 ± 31	48 ± 11	156 ± 58
(n = 15)	6	275 ± 37	45 ± 11	172 ± 58
Mepindolol	0	283 ± 32	45 ± 10	189 ± 60
(n = 14)	6	273 ± 33	45 ± 10	203 ± 61

[a] $p < 0.05$ vs. baseline.

changes in HDL-C induced by the β-blockers were statistically significant with propranolol and atenolol but not with bisoprolol and mepindolol (Fig. 3). The same difference in behavior was valid for the increases in TG, but, however, only in group II (Fig. 4).

As regards blood pressure data, all β-blockers caused a similar decrease in blood pressure values that persisted throughout the follow-up.

DISCUSSION

The results of this study show that, in long-term monotherapy of both normocholesterolemic and hypercholesterolemic hypertensive patients, none of the β-blockers used worsened TC levels, which is in agreement with previous reports in the literature (9,10,23,24). Indeed, in patients with normal pretreatment cholesterol levels, TC tended to decrease from the end of the second year of treatment with any β-blocker, confirming a trend already observed in some major trials of primary prevention (25,26). In patients with basal TC > 220 mg/dl, the tendency toward lower TC levels was more remarkable and already evident after 6 months of therapy. It should be noted, however, that the subjects with high TC values were given dietary advice, while the normal lipid subjects were not, which could have played a role in the different TC behavior over time.

Considering HDL-C and TG, the present study confirmed that the β-blocker pharmacodynamic properties influence the magnitude of the changes in such parameters. Nonselective, non-ISA propranolol caused the most pronounced increase in TG and decrease in HDL-C levels. These alterations were less marked on β_1-selective atenolol and bisoprolol (the latter did not significantly affect HDL-C values throughout the study and increased TG less than atenolol, confirming that the greater the β_1-selectivity, the lesser are the effects of β-blockers on plasma lipids) and even more discrete on mepindolol with ISA (which tended to increase HDL-C, although not significantly).

The β-blocker pharmacodynamic properties seem to be less important in affecting the long-term evolution of the initial changes in HDL-C and TG values. Considering the course over time, the variations in HDL-C and TG values were similarly apparent between 6 months and 1 year of β-blocker monotherapy. Such variations reached their peak in 6–12 months; then, after a plateau phase, they showed a progressive trend to return to values that were increasingly nearer to the pretreatment ones.

The TG and HDL-C changes induced by 6-month β-blocker monotherapy in patients with basal TC > 220 mg/dl were qualitatively similar to those observed in normal lipid subjects (increase in TG and decrease in HDL-C). Again, such changes were less pronounced on β_1-selective and ISA-provided β-blockers. However, the hypercholesterolemic patients showed a lower percentage change in both TG and HDL-C values compared to normocholesterolemic ones. A possible explanation for this unexpected ob-

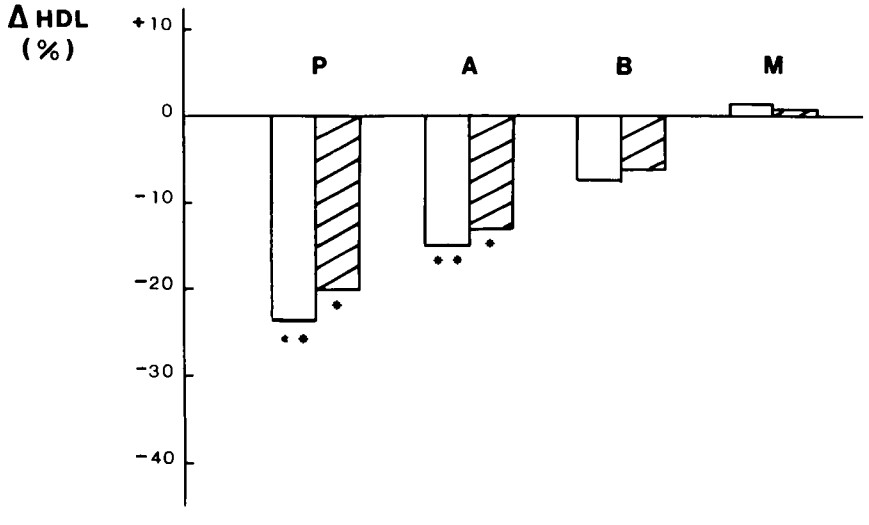

FIG. 3. Percentage changes in HDL-C values after 6 months of β-blocker therapy in normocholesterolemic (□) and hypercholesterolemic (▨) hypertensive patients (P = propranolol, A = atenolol, B = bisoprolol, M = mepindolol). *$p < 0.05$, **$p < 0.01$ vs. baseline.

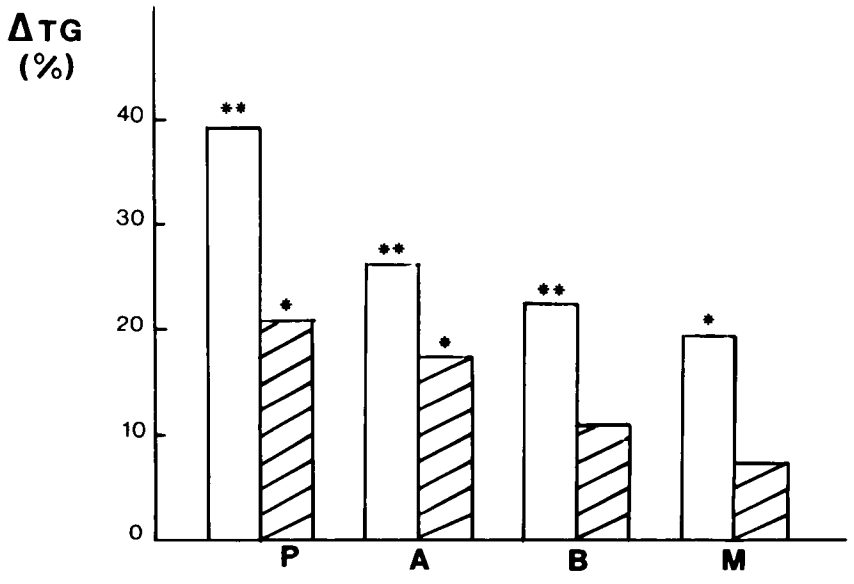

FIG. 4. Percentage changes in TG values after 6 months of β-blocker therapy in normocholesterolemic (□) and hypercholesterolemic (▨) hypertensive patients (P = propranolol, A = atenolol, B = bisoprolol, M = mepindolol). $^{*}p < 0.05$, $^{**}p < 0.01$ vs. baseline.

servation might be that the TG and HDL-C changes induced by β-blockers were very similar, in absolute values, both when their mean pretreatment values were normal and when they were abnormal.

REFERENCES

1. Roberts WC. Blood lipid levels and antihypertensive therapy. *Am J Cardiol* 1987;60:24E–8.
2. Weinberger MH. Antihypertensive therapy and lipids. Evidence, mechanisms and implications. *Arch Intern Med* 1985;145:1102–5.
3. Chait A. Effects of antihypertensive agents on serum lipids and lipoproteins. *Am J Med* 1989;86(suppl 1B):5–7.
4. Weinberger MH. Antihypertensive therapy and lipids. Paradoxical influences on cardiovascular disease risk. *Am J Med* 1986;80(suppl 2A):64–70.
5. Robertson JIS. The large studies in hypertension: what have they shown? *Br J Clin Pharmacol* 1987;24(suppl 1):3S–14.
6. Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial: risk factor changes and mortality results. *JAMA* 1982;248:1465–77.
7. Kuller LH, Hulley SB, Cohen JD, et al. Unexpected effects of treating hypertension in men with electrocardiographic abnormalities: a critical analysis. *Circulation* 1986;73:114–23.
8. Kaplan NM. Importance of coronary heart disease factors in the management of hypertension. *Am J Med* 1989;86(suppl 1B):1–4.
9. Ames RP. The effects of antihypertensive drugs on serum lipids and lipoproteins. II—Non diuretic drugs. *Drugs* 1986;32:335–57.
10. Weidman PW, Uelinger DE, Gerber A. Antihypertensive treatment and serum lipoproteins. *J Hypertens* 1985;3:297–306.
11. Sacks FM, Dzau UJ. Adrenergic effects on plasma lipoprotein. Speculation on mechanisms of action. *Am J Med* 1980;80(suppl 2A):71–81.
12. Castelli WP, Garrison RF, Wilson PF, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels: The Framingham Study. *JAMA* 1986;256:2835.
13. Rose G, Shipley TC. Plasma cholesterol concentration and death from coronary heart disease: 10 year results of the Whitehall Study. *Br Med J* 1986;293:306.
14. Roessner S, Weiner L. A comparison of the effects of atenolol and metoprolol on serum lipoproteins. *Drugs* 1983;25(suppl 2):322–5.
15. Day JL, Simpson N, Metcalfe J, Page RL. Metabolic consequences of atenolol and propranolol in treatment of essential hypertension. *Br Med J* 1979;1:77–80.
16. Fager G, Berglund G, Bondjers G, et al. Effect of antihypertensive therapy on serum lipoproteins: treatment with metoprolol, propranolol and hydrochlorothiazide. *Artery* 1983;11:283–6.
17. Fogari R, Zoppi A, Pasotti C, et al. Plasma lipids during chronic antihypertensive therapy with different β-blockers. *J Cardiovasc Pharmacol* 1989;14(suppl 7):S28–32.
18. Van Brummelen P. The relevance of intrinsic sympathomimetic activity for β-blocker-induced changes in plasma lipids. *J Cardiovasc Pharmacol* 1983;5(suppl 1):S51–5.
19. Pasotti C, Capra A, Fiorella G, Vibelli C, Chierichetti SM. Effects of pindolol and metoprolol on plasma lipids and lipoproteins. *Br J Clin Pharmacol* 1982;13(suppl 2):435S–9.
20. Lehtonen A, Hietanen E, Marniemi J, Peltonen P, Niskanen J. Effect of pindolol on serum lipids and lipid-metabolizing enzymes. *Br J Clin Pharmacol* 1982;13(suppl 2):445S–7.
21. Roschlau P. Enzymatische Bestimmung des Gesamtcholesterin im Serum. *Z Klin Chem Klin Biochem* 1974;12:403.
22. Viikari J. Precipitation of plasma lipoproteins by PEG-6000 and its evaluation with electrophoresis and ultracentrifugation. *Scand J Clin Lab Invest* 1976;36:265.
23. Leren P, Foss OP, Helgeland A, Holme S, Hjermann L, Lund-Larsen PG. Effect of propranolol and prazosin on blood lipids. *Lancet* 1980;2:4.
24. Leon S, Agre J, Grimm R, et al. Plasma lipid change with methyldopa and propranolol during treatment of hypertension. *Circulation* 1982;66(suppl 2):37.
25. Wilhelmsen L, Berglund G, Elmfeldt D, et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens* 1987;5:561–72.
26. Wikstrand J, Warnold I, Olsson G, Tuomilheto J, Elmfeldt D, Berglund G. Primary prevention with metoprolol in patients with hypertension. Mortality results from the MAPHY study. *JAMA* 1988;259:1976–82.