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Effects of Bisoprolol on Lipoprotein Cholesterol Subfractions and Apolipoproteins in Patients with Hypertension

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Non-selective beta-blockers tend to increase triglycerides and low-density lipoprotein (LDL) cholesterol while decreasing the atheroprotective high-density lipoprotein (HDL) cholesterol, particularly the HDL_2 cholesterol subfraction. The aim of this study was to investigate whether the highly $beta_1$-selective beta-blocker bisoprolol shares with non-selective beta-blockers these effects on blood lipids in patients treated for mild or moderate essential hypertension. In particular, HDL cholesterol and its subfractions HDL_2 cholesterol and HDL_3 cholesterol as well as apolipoproteins A1 and B were investigated. In a multicentre outpatient trial, 86 hypertensive patients received bisoprolol for eight weeks. Diastolic blood pressure was reduced from a baseline of 102 ± 7 mmHg (mean ± SD) to 87 ± 8 mmHg after 8 weeks of therapy with bisoprolol. Systolic blood pressure decreased from 159 ± 17 mmHg to 139 ± 14 mmHg. Blood pressure was normalized in 69 % of patients with 5 mg bisoprolol once daily and, after increasing the dosage to 10 mg bisoprolol once daily in non-responders, in 80 % of patients. Treatment with bisoprolol decreased triglycerides by 4.8 % and LDL cholesterol by 1.7 %, whereas HDL cholesterol increased by 5.2 %, which was attributable to an increase by 9.2 % of HDL_2 cholesterol and by 3.0 % of HDL_3 cholesterol, respectively. None of these single changes were significant at the $p < 0.05$ level. Surprisingly, however, all lipid effects were in the favourable direction and opposite to the changes usually observed with non-selective beta-blockers. In a mathematical model derived from angiographic studies, the improvement of lipid risk factors brought about by bisoprolol equalled that of a decrease in age by 3.5 years. We thus conclude that effective antihypertensive doses of bisoprolol do not exert the typical dyslipidaemic effects of beta-blockers but rather tend to induce small but favourable changes in plasma triglycerides, LDL and HDL cholesterol, and especially in the atheroprotective HDL_2 cholesterol subfraction. *J Clin Basic Cardiol 2001; 4: 57–60.*

Key words: bisoprolol, beta-blocker, blood lipids, LDL cholesterol, HDL cholesterol, HDL subfractions, apolipoproteins

A number of lipid risk factors are linked to coronary artery disease (CAD). Levels of plasma total and low density lipoprotein (LDL) cholesterol are directly related to the incidence of CAD [1, 2]. Therapeutic reduction of LDL cholesterol has been proven to reduce coronary morbidity and mortality as well as total mortality, both by primary [3] and secondary prevention trials [4].

High density lipoprotein (HDL) cholesterol on the other hand is inversely related to the incidence of CAD [5–7], which means that HDL cholesterol is associated with protection from atherosclerosis. In the Framingham Heart Study, low HDL cholesterol proved a better predictor of CAD than elevated LDL cholesterol [8]. Indeed, among the various lipid risk factors measured so far, HDL cholesterol has been considered the strongest predictor of CAD [7]. Decreased HDL cholesterol values even predict CAD when total cholesterol values are not elevated [9].

HDL cholesterol is not a uniform lipoprotein class. Human plasma contains three classes with different biochemical properties: HDL_1 which is present only in traces, and the two main subfractions HDL_2 and HDL_3 [10]. We have previously demonstrated that among all lipoprotein parameters measured, low HDL_2 cholesterol is the strongest predictor of both the presence and the extent of coronary atherosclerosis [11, 12].

Lipoproteins are spherical particles whose oily core of nonpolar lipids (cholesteryl esters and triglycerides) is surrounded by a polar layer of phospholipids and apolipoproteins (apos) on the surface. Lipoprotein classes do not only differ from one another by their lipid core, but also by the pattern of apos on their surface. Apoprotein A1 is the main constituent of HDL (both, HDL_2 and HDL_3), and apoprotein B is the main part of LDL, but also present on very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). Because each of the three particle classes, VLDL, IDL and LDL, carries exactly one molecule of apo B per particle, the latter is a measure for the total number of VLDL, IDL, and LDL particles. Although apo A1 does not show this exact molar ratio of one molecule per particle, apo A1 is a good correlate for the total number of HDL particles. Direct measurement of apos A1 and B has therefore been used to estimate the particles' number rather than their lipid content.

Beta-blockers are widely used to treat cardiovascular diseases. These compounds tend to increase triglycerides and LDL cholesterol and to decrease HDL cholesterol and, particularly, HDL_2 cholesterol [13, 14]. These unfavourable effects on lipid metabolism could increase the vascular risk and could therefore partly counterbalance the multiple beneficial effects of beta-blockers in atherosclerotic cardiovascular disease. The magnitude of the dyslipidaemic effect seems to depend on the degree of $beta_1$-selectivity of a beta-blocker; non-selective beta-blockers have a greater effect on plasma lipids than $beta_1$-selective blockers [15]. It is thus not surprising that for the highly $beta_1$-selective blocker bisoprolol no major effects on triglycerides, total cholesterol, LDL cholesterol or HDL cholesterol have been reported so far [16–18]. However, bisoprolol's actions on HDL subfractions cholesterol (HDL_2 and HDL_3 cholesterol), as well as on apo A1 and B are not known. The aim of the present study thus was to investigate the effects of bisoprolol on these powerful and specific markers of atherosclerotic risk.

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Methods

Patients

The study was conducted by general practitioners in Switzerland as a multi-centre outpatient study. After informed written consent had been obtained, patients with mild to moderate essential hypertension were enrolled into the study if they fulfilled two criteria: (a) mean sedentary diastolic blood pressure at > 2 blood pressure readings of > 90 mmHg, and (b) no severe organ damage due to longstanding hypertension. Criteria for excluding patients were: contraindications for beta-blockers, renal or hepatic dysfunction, history of stroke or myocardial infarction within the preceding 6 months, pregnancy and lactation. Concomitant use of other drugs that could affect the serum lipids was avoided during the study, in particular no diuretics or drugs affecting lipid metabolism were used. Also, no other antihypertensive drugs were allowed during the trial. If a patient had already taken antihypertensives before the study, the drugs were discontinued 4 weeks prior to the onset of the protocol.

Prior to the onset of treatment, a lipid profile was obtained, which included measurements of the plasma concentrations of triglycerides, cholesterol, HDL cholesterol, HDL_2 and HDL_3 cholesterol subfractions, LDL cholesterol, and apo A1 and apo B. Serum creatinine and serum potassium were also measured before and after treatment, and sedentary blood pressure and heart rate were recorded.

Biochemical methods

Lipid and lipoprotein measurements were performed as previously described [11]. In short, after an overnight fast and complete abstinence from ethanol for 12 hours, venous blood was drawn without the use of a tourniquet in a sitting position. Plasma was frozen immediately after centrifugation and stored at –20 °C. The frozen samples were collected from all participating physicians by a courier within 5 days and transported in a container at –20 °C to the analysing center. Only non-haemolytic plasma samples were further processed; patients whose plasma samples were haemolytic were excluded from the analysis.

Cholesterol and triglycerides were measured enzymatically using the cholesterol CHOD-PAP method and the triglyceride GPO-PAP method, respectively. HDL cholesterol, HDL_2 cholesterol and HDL_3 cholesterol were determined using a stepwise precipitation procedure with dextrane sulphate [19, 20]. The results obtained by this stepwise HDL cholesterol precipitation procedure are easily comparable to those obtained by HDL cholesterol subfraction analysis using rate zonal ultracentrifugation [10]. Plasma concentrations of apos A1 and B were determined by turbidimetric immunoprecipitation assays (Uni Kit T, Roche) on a Cobas Mira. These methods have been shown to give excellent agreement with nephelometric assays [21]. LDL cholesterol was calculated [22].

Table 1. Clinical characteristics of patients

Parameter	Means ± SD
Age (years)	54 ± 12
Body length (cm)	169 ± 8
Body weight (kg)	76 ± 13
Body mass index (kg × m^{-2})	26.5 ± 3.6

Table 2. Effects of 8 weeks of treatment with bisoprolol on serum potassium, creatinine, blood pressure and heart rate

Parameter	Before treatment	After treatment
Serum potassium (mmol/l)	4.5 ± 1.6	4.3 ± 0.5
Serum creatinine (μmol/l)	86 ± 18	85 ± 17
Systolic blood pressure (mmHg)	159 ± 17	139 ± 8*
Diastolic blood pressure (mmHg)	102 ± 7	87 ± 8*
Heart rate (min^{-1})	76 ± 9	67 ± 9*

* statistically significant differences

Table 3. Effect of 8 weeks of treatment with 5–10 mg bisoprolol daily on lipid parameters

Parameter	Mean before treatment	Mean after 8 weeks of treatment	Mean of intraindividual differences*
Triglycerides (mmol/l)	1.83	1.74	–0.087
Cholesterol (mmol/l)	5.71	5.68	–0.025
LDL-C-cholesterol (mmol/l)	3.71	3.66	–0.064
HDL cholesterol (mmol/l)	1.20	1.26	+0.062
HDL_2 cholesterol (mmol/l)	0.26	0.28	+0.024
HDL_3 cholesterol (mmol/l)	1.12	1.15	+0.034
apo A1 (g/l)	1.55	1.55	±0.000
apo B (g/l)	1.21	1.22	+0.013

* all single differences were non-significant

Treatment

Bisoprolol was administered once daily as a 5 mg tablet in the morning at an initial dose of 5 mg/day. If blood pressure was not lowered to values ≤ 155/90 mmHg within two weeks, the dosage of bisoprolol was increased to 10 mg/once daily in the morning. Treatment was continued for a total of eight weeks. During the study the patients were regularly interviewed for the presence of subjective symptoms or adverse reactions.

At the end of the study blood pressure and heart rate were recorded and measurements of lipid parameters, serum creatinine and serum potassium were repeated.

Lipid formula

The amount of atherosclerosis in the coronary tree can be quantitated as the extent of coronary atherosclerosis (ie the number of lesions with ≥ 50 % narrowing). The quantitative interrelation of risk factor levels (eg age, lipids, etc.) with the extent of disease can be determined as recently reported [12]. Then the effects of the various lipids and of age on the disease extent are compared. The amount of a given lipid, that increases disease extent by the same amount as an age increase of one year, can be standardized as an age-equivalent of 1 year. The age equivalents of 1 year are: an increase by 0.092 mmol/l of LDL cholesterol, by 0.101 mmol/l of triglycerides, as well as a decrease by 0.020 mmol/l of HDL_2 cholesterol and by 0.046 mmol/l of HDL_3 cholesterol, respectively. In the present study the changes of the various lipids observed after 8 weeks of bisoprolol treatment were entered into the formula to obtain the total age equivalent of the lipid effects brought about by bisoprolol.

Statistical analysis

Values before and after 8 weeks of therapy were compared using a t-test for paired data with a level of significance set at $p < 0.05$.

Results

A total of 86 patients (46 men, 40 women) were included into the analysis. Clinical characteristics of patients are summarized in Table 1. Effects of treatment on serum potassium, creatinine, and blood pressure are given in Table 2.

Lipid effects

Levels of blood lipids obtained before and at the end of the study are summarized in Table 3 and Figure 1. There was no

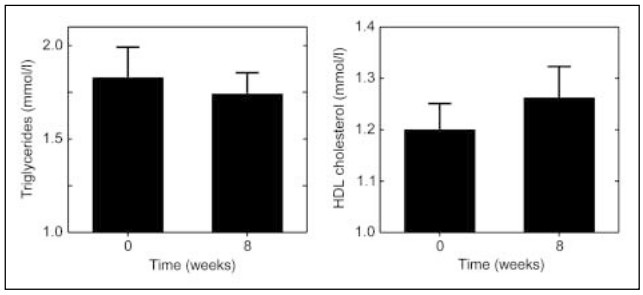

Figure 1. Plasma levels of triglycerides and HDL cholesterol before and after 8 weeks of treatment with bisoprolol (means, bars indicate SEM)

adverse effect on plasma triglycerides or cholesterol, LDL cholesterol, total HDL cholesterol, HDL_2 cholesterol, HDL_3 cholesterol, apo A1 or apo B. A non-significant trend towards lower triglycerides and LDL cholesterol as well as towards higher HDL_2 cholesterol and HDL_3 cholesterol (and, thus, HDL cholesterol) values was observed. When entered into the angiographic lipid formula, the mean reductions of LDL cholesterol by 0.064 mmol/l (see Table 3) and of triglycerides by 0.087 mmol/l equalled a reduction of coronary atherosclerosis risk by 0.86 and 0.70 year equivalents, respectively. The mean increases of HDL_2 cholesterol by 0.024 mmol/l and of HDL_3 cholesterol by 0.034 mmol/l equalled a further reduction in age equivalents by 1.20 and 0.74 years, respectively. Thus, a total of 3.5 year equivalents were gained by treatment with bisoprolol.

Haemodynamic effects

At baseline, average (± SD) blood pressure was 159/105 (± 19/± 7) mmHg and heart rate was 76 (± 9) min^{-1}. After two weeks of treatment, diastolic blood pressure was at or below 90 mmHg in 59 patients (69 %). In the 27 patients whose diastolic blood pressure was still above 90 mmHg, bisoprolol was increased to 10 mg once daily. After another 6 weeks of treatment, 10 of the 27 patients had diastolic blood pressure readings of 90 mmHg or less. Considering also these 10 patients with adequate blood pressure control under 10 mg bisoprolol per day, diastolic blood pressure was normalized in 69 (80 %) of the patients. Average systolic blood pressure was 139 ± 14 mmHg and diastolic blood pressure was 87 ± 8 mmHg at the end of the study. Heart rate was reduced from 76 ± 9 to 67 ± 9 min^{-1}. Thus average reduction of systolic blood pressure was 20 mmHg, average reduction of diastolic blood pressure was 18 mmHg, and heart rate was reduced at average by 9 min^{-1}.

All but 2 patients completed the study (drop out rate 2.3 %). Minor side effects like fatigue were reported by a total of 12 patients (14 %), no serious adverse events were observed during the study.

There were no significant changes of serum creatinine or serum potassium levels after 8 weeks of bisoprolol treatment.

Discussion

The data of the present study demonstrate that bisoprolol, administered at a daily dose of 5 to 10 mg, sufficiently controlled hypertension in about 80 % of patients. At this dosage, bisoprolol had no adverse effects on total plasma cholesterol or triglycerides, LDL cholesterol, HDL cholesterol, HDL_2 cholesterol, HDL_3 cholesterol, or on apo A1 or apo B. That plasma levels of apo A1 and B remained constant, indicates that there was no change in the number of particles in the VLDL+IDL+LDL range or in the HDL range. Bisoprolol proved even superior to traditional $beta_1$-selective blockers in that it had not only no adverse influence on lipid metabolism, but rather induced a favourable trend in triglycerides, LDL cholesterol, HDL cholesterol, and in its two subfractions, HDL_2 and HDL_3 cholesterol. Quantitative data derived from our angiographic lipid formula indicate that the grand total of lipid effects brought about by bisoprolol decreased the risk for coronary atherosclerosis by the same amount as a decrease in age by 3.5 years. It should, however, be kept in mind that this "gain" of 3.5 years refers to an amount of angiographic extent of coronary atherosclerosis and does not mean automatically that clinical morbidity or mortality are postponed by 3.5 years.

These data agree well with and extend the findings of previous studies that found that bisoprolol did not adversely influence total cholesterol, HDL cholesterol, or LDL cholesterol [16–18]. Frithz and Weiner reported that bisoprolol had no undesirable effects on total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides in 42 patients studied over 10 months [16]. Fogari et al. reported from a study with a follow-up of three years that bisoprolol did not adversely affect HDL cholesterol or triglycerides, while propranolol and atenolol both deteriorated these lipid parameters [17].

The mechanisms by which beta-blockers usually lower HDL cholesterol levels and increase plasma triglycerides is not firmly established. One explanation is that beta-blockade leaves naturally occurring alpha-adrenergic stimulation unopposed. Predominant alpha stimulation decreases the activity of lipoprotein lipase, the key enzyme of triglyceride hydrolysis, whereas the enzyme would be activated by stimulation of $beta_2$ receptors [23, 24]. Low lipoprotein lipase activity in turn leads to an accumulation of plasma triglycerides and a concomitant decrease of HDL cholesterol, specifically HDL_2 cholesterol as was observed for beta-blockers [15]. In one trial, propranolol reduced HDL_2 cholesterol by 38 % and also reduced apo A1 [25]. Thus, the lipid changes typically seen with non-selective beta-blockers can be readily explained by the catecholamine-induced alpha-receptor mediated inhibition of lipoprotein lipase activity [23].

While the adverse changes of lipid metabolism are very pronounced with non-selective beta-blockers, they have also – although to a lesser extent – been observed with beta-blockers that preferentially inhibit $beta_1$-adrenoreceptors like metoprolol and atenolol [17]. Day et al. compared the effects of the 4 beta-blockers atenolol, metoprolol, oxprenolol and propranolol on blood lipids [23]. All of them increased total triglyceride levels and reduced HDL cholesterol. Reduction of HDL cholesterol was clearly dependent on the $beta_1$-selectivity: Baseline HDL cholesterol of 1.31 mmol/l was reduced to 1.22 mmol/l on atenolol, to 1.14 mmol/l on metoprolol, to 1.16 mmol/l on oxprenolol and to 1.09 mmol/l on propranolol. Thus, although the decrease of HDL cholesterol with the $beta_1$-selective agents atenolol and metoprolol is less pronounced it is still significant [23]. Substances like bisoprolol (that does not block $beta_2$-receptors) or celiprolol (that has a mild $beta_2$-stimulating action) would not negatively interfere with lipoprotein lipase activity and thus can be expected not to deteriorate triglycerides or HDL. Our data clearly support this concept. A large body of literature also underlines this view. In a comparative study with propranolol and atenolol over 18 months, bisoprolol affected the triglycerides less than propranolol or atenolol and had no significant effect on HDL cholesterol levels. Total cholesterol and LDL cholesterol were not affected significantly either [17, 18]. Taken together, thus, the lipid-neutral effects of bisoprolol apparently are a consequence of the high $beta_1$-selectivity of the compound.

Our study also demonstrated a potent antihypertensive effect and high safety of bisoprolol in patients with mild to moderate hypertension. About 69 % of the patients were sufficiently treated by 5 mg of bisoprolol daily. Increasing the dosage to 10 mg bisoprolol daily resulted in an overall response rate of about 80 %. No serious adverse events were reported. Minor side-effects were reported by 14 % of the patients, but drop-out rate was only around 2 %.

In conclusion, thus, bisoprolol is an effective antihypertensive drug that is well tolerated by most patients. There is a slight beneficial influence of bisoprolol on the lipid fractions measured. Hence bisoprolol appears rather to decrease than to increase the lipid-mediated risk for developing or accelerating coronary atherosclerosis.

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Appendix

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