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ORIGINAL ARTICLE

Effects of celiprolol and simvastatin on the calculated risk of coronary heart disease (the Celisimva study)

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Abstract

Objectives. The most important risk factors for coronary heart disease are hypercholesterolemia, smoking and hypertension. To find out which treatment is more effective in modifying the total risk – lowering cholesterol concentration or using antihypertensive treatment – we conducted a parallel group placebo-controlled study. The goal of the study was to assess the effect of two drugs on the calculated CHD Framingham risk score in subjects with both moderate hypertension and moderate hypercholesterolemia. *Design*. Celiprolol for hypertension and simvastatin for cholesterol-lowering were given as monotherapy or as combination treatment. The effects of the treatments on the CHD risk scores were calculated after 3 months. A total of 112 patients were randomized. *Results*. The total CHD risk decreased in simvastatin and combination groups from 26% to 19% and from 26% to 17%, respectively. Celiprolol alone decreased the risk from 25% to 21%, which was not statistically different from placebo. *Conclusions*. It can be concluded that subjects with moderate hypercholesterolemia and hypertension benefit more from lipid-lowering treatment with simvastatin than from blood pressure-lowering with beta blocker celiprolol.

Key words: *Celiprolol, simvastatin, hypertension, hypercholesterolemia, coronary risk*

Introduction

The three most important, classic risk factors of coronary heart disease (CHD) are high concentration of LDL cholesterol, smoking and hypertension (1). Subjects with several risk factors (clustering of risk factors) have a higher risk than those with only one factor. In various international or national guidelines for treatment of hypertension and hypercholesterolemia (2,3) the clinician is urged to estimate the total cardiovascular risk of the patient before making treatment decisions. Decision-making is usually based on epidemiological studies that predict the risk of an end-point for example the risk of coronary heart disease or mortality during 5 or 10 years of follow-up (3–7).

Perhaps the most widely used tool is the risk equation developed from the database of Framingham heart study (3). The equation uses several risk factors such as age, gender, systolic blood pressure, serum total cholesterol, serum high density lipoprotein cholesterol, smoking, glucose intolerance and left ventricular hypertrophy. The equation is based on follow-up of the population of a small town in the US and there has been some criticism concerning its reliability in other populations. The equation is not based on an intervention study but is has been tested in such a study on Scottish population (8). According to that comparison it was concluded that the Framingham risk profile calculator and tables can be used to estimate the effect of the treatment on the total cardiovascular risk profile. An updated version of the risk profile has been published in 1991 [3]. Recently it was reported that the Framingham coronary risk score significantly overestimates the actual absolute coronary risk in British men (7) and a BMJ editorial emphasizes that prediction algorithms need regular updating (9).

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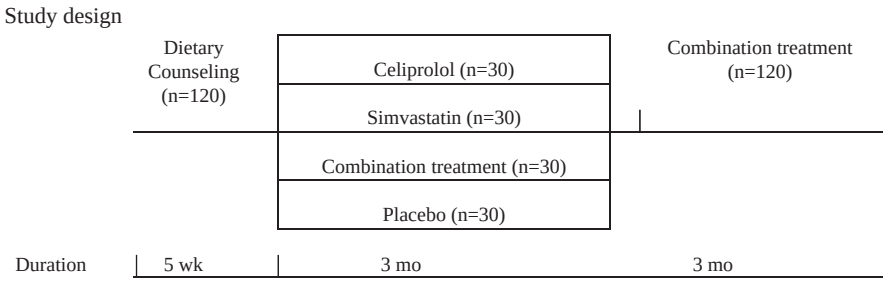

Figure 1. Study design and different time points during the study. After a 5 week run-in period the patients were randomized to one of the four groups receiving the study medication. The main study period was 3 months. After that all the groups received the combination treatment (celiprolol + simvastatin) for another 3 months.

Most intervention studies aim to investigate the effect of pharmaceutical treatment to one of the risk factors, usually either hypertension or dyslipidaemia. Very few studies have been conducted that aim to investigate the effect of multiple risk factor intervention (10,11).

In the ASCOT-LLA study published recently (12), however, one of the objectives was to evaluate whether synergistic effects on total coronary or cardiovascular events are observed in association with the combined use of a cholesterol-lowering agent and an antihypertensive drug.

It is often difficult to decide in clinical practice whether hypertension or dyslipidaemia should be the primary target of pharmacological treatment in a patient with mild hypertension and mild hypercholesterolemia. There is convincing evidence that both conditions have to be treated because treatment of either of the two results in reduction of cardiovascular end-points in the follow-up (13–17).

It would be useful for the clinician to have background information about the differences between various drugs and about the combined effect of two different types of drugs such as a cholesterol-lowering drug and an antihypertensive drug, in their ability to reduce the calculated overall risk, total burden of the most important risk factors for cardiovascular diseases.

Objectives

To find out which one – antihypertensive treatment or lowering cholesterol concentration – is more effective in modifying the total cardiovascular risk, we conducted a parallel group placebo-controlled study.

The goal of the study was to assess the effect of two different drugs on the total calculated CHD risk score in subjects with both moderate hypertension and moderate hypercholesterolemia.

Design

The drugs chosen were celiprolol for the treatment of hypertension and simvastatin for lowering the cholesterol concentration. They were given either as monotherapy or as combination treatment. The effects of the treatments on the CHD risk scores were calculated after 3 months of use, and the risk scores were compared with those at baseline (Figure 1).

The antihypertensive drug used in the study was celiprolol, a cardioselective beta-blocking agent with mild intrinsic sympathomimetic activity and moderately positive effects on plasma lipids. Celiprolol is claimed to increase the concentration of HDL cholesterol and to decrease the concentration of triglycerides moderately as well as to have a beneficial effect on insulin sensitivity associated with the metabolic syndrome (18). Simvastatin inhibits cholesterol synthesis at the rate-limiting step by inhibiting the enzyme HMG-COA-reductase and reduces the concentration of serum LDL cholesterol. It also increases the concentration of HDL cholesterol and decreases the concentration of serum triglycerides, all beneficial effects with respect to the cardiovascular risk (19).

Subjects

Patients included in the study were men and women with high CV risk aged between 50 and 70 years at randomisation, free of CHD with untreated systolic hypertension, defined as systolic blood pressure over 140 mmHg, hypercholesterolaemia, defined as a total serum cholesterol concentration over 5.5 mmol/l. Their 10-year CHD risk should be above 20% as calculated according to the updated Framingham equation (3). The body mass index had to be below 35. The women had to be postmenopausal, and eventual hormone replacement therapy had to remain unchanged before and during the study. Patients with type 2 diabetes were included if

their B-GHb-A1C was below 10% and if their medication was assumed to remain stable. Smokers were included, in the risk calculations smoking habits were considered unchanged during the study although the participants were strongly advised to stop smoking.

Exclusion criteria included coronary heart disease, left ventricular hypertrophy diagnosed by electrocardiagram, current medication for hypertension or hypercholesterolemia or medication during the past month, serious chronic disease, unstable asthma, newly diagnosed type 2 diabetes. Patients were excluded from the study if their total serum cholesterol was 9 mmol/l or more, systolic blood pressure 180 mmHg or more or the calculated CHD risk score was 40% or more after the 5-week run-in period.

Interventions

Investigators at the selected study sites (total number of sites 20) recruited volunteers mainly by using advertisements in local newspapers. The plan was to recruit a total of 120 patients, 30 in each of the four treatment groups. Volunteers that were suitable for the study gave written consent and were entered into the 5-week run-in period. The patients were given spoken and written dietary advice and after the run-in period their blood pressure was measured and fasting blood samples were taken to determine serum lipid concentrations. After this baseline visit patients included in the study were randomized in one of the four groups receiving either a single dose of 200 mg celiprolol (in the morning), 10 mg simvastatin (in the evening), combination treatment or placebo. In order to keep the study blind, double-dummy technique was used. Thus, there was a placebo for both celiprolol and simvastatin. All the patients took two tablets daily throughout the study.

The first 3 months of treatment formed the above-mentioned, double-blind phase of the trial. After 3 months blood pressure and lipids were measured and the total cardiovascular risk was calculated. After that all the patients received combination treatment for another 3 months (open label phase of the study). At the end of the study, the total risk score was calculated again. The motivation for this combination treatment was to get informaton on compliance, efficacy and tolerability of combinaton treatment vs. monotherapy with either of the drugs.

The CHD risk score (%), based on the formula from the Framingham study (3), was the primary efficacy parameter. The calculated 10-year risk equation used the following variables: age, gender, smoking, diabetes, systolic blood pressure and serum total and HDL cholesterol. Blood pressure was measured by a trained study nurse (one per study center) with a mercury sphygmomanometer. Blood pressure was measured three times at 2-minute intervals, and the mean of the last two measurements was recorded. Serum cholesterol and HDL cholesterol as well as other laboratory tests were measured at a core laboratory (Medix, Espoo)

It was estimated that 23 patients per treatment group would be a sufficient sample size to detect a 20% change in the mean CHD-risk score during the study. The calculation was based on information obtained from a random sample ($N = 100$) derived from Finriski-97 data which was maintained by the National Public Health Institute of Finland (20).

Results

A total of 481 patients were screened, out of which 159 patients met the inclusion criteria at screening. A total of 112 patients were randomized to receive the double blind treatment, 4 patients were withdrawn during the first 3-month phase of the trial and another 2 patients during the second 3-month phase. A total of 106 patients participated in the whole study.

Although both genders were included, the vast majority (95%) of the participants were male. The total amount of female subjects was only 6 patients. The mean age of the participants was 61 years.

The baseline characteristics of the patients are described in Table I.

All randomized patients were included in the intent-to-treat analysis when it was technically possible.

All treatments were reasonably well tolerated. There were no major serious adverse events that led to discontinuation of study medication. Participitation in the study was interrupted due to adverse events in four cases. Of these myalgia was reported to have a definite relationship to the study drug and arrhythmia was reported to have a possible relationship to the study drug. No laboratory abnormalities were reported as serious.

Systolic blood pressure was similar in all groups at baseline ranging from 156 to 161 mmHg ($p = 0.4865$). Systolic blood pressure decreased significantly only in the celiprolol group, from the mean value of 158 mmHg at baseline to 147 mmHg after 3 months of treatment ($p = 0.0030$). At the end of the study, after the phase of combination treatment in all groups, the mean systolic pressure had decreased significantly.

Diastolic blood pressure was also similar in all groups at baseline ranging from 92 to 95 mmHg, There was a small decrease in all groups at 3 months (-1 to -5 mmHg),

Table I. Baseline characteristics.

Characteristic	Group			
	Celiprolol n = 27	Simvastatin n = 27	Combination n = 29	Placebo n = 29
Sex (n):				
Male	26	26	27	27
Female	1	1	2	2
Age (years)	60 ± 6	61 ± 6	60 ± 7	62 ± 6
BMI (kg/m^2)	27 ± 2	28 ± 3	28 ± 3	26 ± 3
Smoking (n):				
Smoker*	11	12	16	15
Non-smoker	16	15	13	14
Type 2 diabetes (n)	3	2	3	2

BMI = Body mass index; * = Smoking at screening or quitted smoking less than 12 months prior screening.

The concentration of total cholesterol decreased significantly in both the simvastatin and combination treatment groups, from 6.9 to 5.2 mmol/l ($p < 0.0001$) and 6.6 to 4.9 mmol/l ($p < 0.0001$), respectively. There was no significant change in the celiprolol or placebo group. After the open phase combination treatment at the end of the study the mean reduction in total cholesterol concentration compared to baseline was 1.8 mmol/l with no differences between the groups.

Table II. Effect of treatments on total CHD risk, blood pressure and lipids at 3 and 6 months compared to baseline (0 mo).

Characteristic	Group			
	Celiprolol n = 27	Simvastatin n = 27	Combination n = 29	Placebo n = 29
Coronary heart disease risk (%)				
0 mo	24.0 ± 3.1	26.0 ± 4.7	25.7 ± 5.0	25.3 ± 6.2
3 mo	21.2 ± 3.3	18.7 ± 3.7	17.3 ± 5.3	25.0 ± 6.4
6 mo*	15.7 ± 3.1	17.1 ± 3.5	16.7 ± 5.3	17.0 ± 4.8
Systolic blood pressure (mmHg)				
0 mo	158 ± 10	156 ± 12	160 ± 12	161 ± 12
3 mo	147 ± 14	152 ± 10	154 ± 15	156 ± 15
6 mo*	146 ± 16	142 ± 10	147 ± 16	147 ± 15
Diastolic blood pressure (mmHg)				
0 mo	93 ± 10	93 ± 9	95 ± 7	95 ± 9
3 mo	90 ± 10	91 ± 7	90 ± 7	92 ± 9
6 mo*	87 ± 11	86 ± 8	87 ± 7	88 ± 9
Total cholesterol (mmol/l)				
0 mo	6.7 ± 0.6	6.9 ± 0.7	6.6 ± 0.8	6.8 ± 0.9
3 mo	6.6 ± 0.9	5.2 ± 0.8	4.9 ± 0.6	6.5 ± 1.0
6 mo*	5.1 ± 0.7	5.1 ± 0.5	5.0 ± 0.8	4.9 ± 0.8
Low density lipoprotein cholesterol (mmol/l)				
0 mo	4.7 ± 0.6	4.7 ± 0.7	4.4 ± 0.8	4.6 ± 0.8
3 mo	4.5 ± 0.8	3.2 ± 0.7	2.8 ± 0.6	4.3 ± 0.8
6 mo*	3.1 ± 0.6	3.1 ± 0.6	2.9 ± 0.9	2.8 ± 0.6
High density lipoprotein cholesterol (mmol/l)				
0 mo	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.4 ± 0.5
3 mo	1.2 ± 0.2	1.3 ± 0.3	1.3 ± 0.2	1.3 ± 0.3
6 mo*	1.3 ± 0.2	1.2 ± 0.3	1.3 ± 0.3	1.3 ± 0.3
Triglycerides (mmol/l)				
0 mo	2.1 ± 1.7	2.3 ± 1.4	2.2 ± 0.9	1.8 ± 0.8
3 mo	2.1 ± 1.7	1.6 ± 0.9	1.9 ± 1.3	2.0 ± 1.0
6 mo*	1.6 ± 0.8	1.6 ± 0.6	1.7 ± 0.9	1.6 ± 0.8

* all groups on combination treatment.

The concentration of LDL cholesterol was reduced significantly in both the simvastatin and combination treatment groups, from 4.7 to 3.2 mmol/l ($p < 0.0001$) and from 4.4 to 2.8 mmol/l ($p < 0.0001$), respectively. There was no significant change in the celiprolol or placebo group. After the open phase combination treatment period at the end of the study, the mean reduction in LDL-cholesterol concentration was 1.6 mmol/l with no differences between the groups.

There was no significant change in the concentration of HDL cholesterol and triglycerides in any of the groups after 3 months of treatment.

At baseline the mean total 10-year risk of CHD was 26.3% with no significant differences between the four groups. The total CHD risk decreased in the simvastatin and combination groups from 26% to 19% ($p < 0.0001$) and from 26% to 17% ($p < 0.0001$), respectively. Celiprolol alone decreased the risk from 25% to 21% ($p = 0.0363$), which was, however, not statistically different from the effect of placebo (25% at baseline and 3 months ($p = 0.1809$)).

After the open label part of the study, the total risk in the whole population was 8.8 percentage units lower than at baseline. There were no significant differences between the groups at this point. In simvastatin and combination treatment groups, the total risk value did not decrease from the value seen at the first three-month timepoint which shows that a three-months treatment period can bring out the whole effect of the treatment (Figure 2).

Discussion

The patients in this study were typically mostly male with characteristics of the metabolic syndrome (hypertension, dyslipidaemia and high BMI). This kind of patients are in a need for primary preventive measures and they pose a challenge for the physician. The most important measures would be to change their life style with dietary factors and physical exercise and in case of smokers to stop smoking. Also when several risk factors cluster, pharmacological measures are needed at an early stage. Patients who responded well to non-pharmacological measures were excluded from this study and only those who were in real need of medication were randomized.

The doses used were pre-fixed and not titrated and thus the recommended starting dose for primary prevention with both drugs was used throughout the study. This explains the moderate effect of celiprolol on blood pressure. Titrating to a larger dose woul probably have increased the antihypertensive effect and, consequently, the effect on the total risk. Simvastatin reduces serum cholesterol concentration more effectively when larger doses are used, each doubling of the dose increasing the LDL cholesterol lowering by approximately 5-6 percentage units (19). In intervention studies, the lowering of total cholesterol concentration by 1 mmol/l maintained over a period of 5 years corresponds to approximately 25–35% lower CHD risk (21). Our findings are in line with this observation.

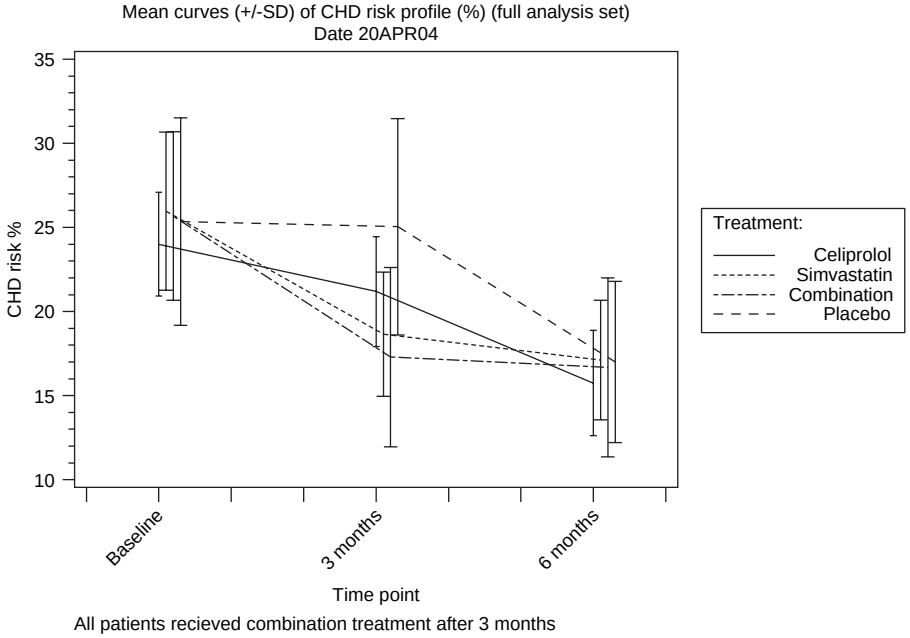

Figure 2.

There was a significant decrease in the total CHD risk score with simvastatin and combination treatments, but not with celiprolol alone. The most effective risk reduction was achieved with the combination of both an antihypertensive and a cholesterol-lowering agent. This combination was also well tolerated. The beta-blocking agent celiprolol had no negative effects on plasma lipids, but no positive effects were detected either.

In the ASCOT-BPLA study (22) the patients were hypertensive with two or more additional risk factors and they were randomized to either a therapy based on a beta-blocking agent or therapy based on calcium-channel blocking with amlodipine. The estimated baseline CHD risk of the patents was approximately 17%. In the randomized and controlled lipid-lowering arm of the ASCOT study there was a 36% reduction in primary end points (nonfatal MI and fatal CHD) in those study subjects who received 10 mg of atorvastatin in comparison to placebo. Also strokes were reduced by 27%. There was no difference in BP, but because all received antihypertensive treatment the baseline BP of 164/95 mmHg was reduced to 138/80 which is a 26 mmHg reduction in systolic blood pressure. In spite of effective blood pressure lowering, there was much room for further reduction in end points, which was actually well demonstrated in the ASCOT-LLA study (12).

Some limitations to our study deserve attention. The Framingham risk score has been criticized. There are some limitatons to its reliability but until now it has been the most widely used tool in CHD risk estimation. The results of an epidemiological study such as Framingham Heart Study should be cautiously used when evaluating effects of treatments. The new SCORE risk estimate which is based on European populations may offer a more reliable tool for risk scoring. This is can be seen after studies conducted with it are published.

When the SCORE risk calculator (23) and the mean values of the different groups (systolic blood pressure and total cholesterol concentration) are used, the baseline 10 year CVD mortality risk of the study patients was 10 to 11%. The estimated mortality risk was reduced to 8, 7, 7 and 9% in the celiprolol, simvastatin, combination treatment and placebo group respectively. After the 6 months' combination treatment for all groups the calculated risk of CVD death was reduced to 6%. These calculations show that with a relatively small statin and antihypertensive dose the total cardiovascular risk is reduced markedly.

The choice of antihypertensive drug can be criticized. In the HOPE study, the ACE-inhibitor ramipril reduced CHD incidence by 25% (24). In the ASCOT-BPLA study treatment based on a calcium blocker and an ACE inhibitor was more effective in reducing CHD events than treatment based on a beta blocker and diuretic (22). Also in the LIFE study angiotensin receptor blocker losartan was more effective than beta blocker atenolol (25). A combination of 2 or 3 antihypertensive drugs is usually needed for effective blood pressure control. The beta blocker celiprolol has intrinsic sympathomimetic activity (ISA) and is usually perhaps not the first choice of treatment. It was chosen for this study because of claims concerning its additional beneficial effects on plasma lipids.

Our study was of a relatively short duration. It can, however, be assumed that the effects of the treatments on blood pressure and plasma lipids that could be achieved during this time, were reached.

Although our aim was to have a relevant number of female participants, almost all subjects were male. This was due to the fact that in women of this age group moderately elevated blood pressure and cholesterol values do not raise the CHD risk sufficiently to be included in this study. To be included, most of the screened women would have had to been both smokers and diabetics as well. And this – fortunately – is quite rare.

Conclusions

Simvastatin (10 mg daily) is more effective than celiprolol (200 mg daily) in reducing the total CHD risk of patients with both moderate hypertension and moderate hypercholesterolemia. Both of these are well tolerated in short term use, both alone and in combination.

In our experience, it has been traditional in health care to first consider hypertension as a target for pharmacological treatment and moderate hypercholesterolemia only after this. This must be due to the fact that landmark studies concerning the treatment benefits for hypertension have been published approximately 20 years earlier than studies concerning the treatment of hypercholesterolemia. Also, treatment guidelines for hypertension have been published earlier. It can be concluded from the results of our study that subjects with moderate hypertension and hypercholesterolemia benefit more from lipid lowering treatment with simvastatin than from blood pressure lowering with beta blocker celiprolol. Thus, treatment of hypercholesterolemia should have higher priority when treating this kind of patients.

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