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Long-term experience (6 years) with simvastatin in patients with heterozygous familial hypercholesterolaemia

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Abstract

Objective: To study the long-term efficacy and safety of the cholesterol synthesis inhibitor, simvastatin, in the treatment of familial hypercholesterolaemia.

Methods: This is an open long-term follow-up of patients treated for 5 years or more in the Nijmegen University lipid clinic. Forty-four patients with heterozygous familial hypercholesterolaemia (mean baseline serum cholesterol level 11.5 mmol/l) were treated with simvastatin alone (monotherapy group) in doses ranging from 20 to 80 mg/day, or in combination with other lipid-lowering agents (combination-therapy group).

Results: Over the intervention period of 6 years the mean overall reduction of the serum cholesterol level was 37.8% for the total group, 37.7% for the monotherapy group and 42.6% for the combination-therapy group. The reduction of the low-density lipoprotein (LDL)-cholesterol in the three groups was 45.0, 44.6 and 50.3%, respectively. The serum triglyceride concentration was reduced by 14.0, 20.5 and 12.5%, respectively. The increase in the high-density lipoprotein (HDL)-cholesterol level was 14.4, 16.2 and 14.0%, respectively. One patient died from a myocardial infarction and 2 patients had a non-fatal cardiac event. Two patients stopped taking medication due to side-effects (dizziness and insomnia). Biochemical adverse effects were confined to elevations of the alanine aminotransferase level and the creatine phosphokinase level and did not lead to discontinuation of therapy.

Conclusions: Simvastatin proves to be a safe and effective lipid-lowering drug during long-term treatment.

Keywords: HMG-CoA reductase inhibitors; Cholesterol; Hyperlipidaemia

1. Introduction

A high serum cholesterol level is a major risk factor for the development of coronary heart disease [1]. Intervention studies with diet and

drugs have shown that lowering the concentrations of total and low-density-lipoprotein (LDL) cholesterol in the blood can reduce the risk of coronary heart disease and arrest the progression of atherosclerotic lesions [2,3]. Patients with familial hypercholesterolaemia (FH) are especially at high risk of premature atherosclerosis [4]. Subjects heterozygous for this disorder have only half the normal amount of high-affinity receptors for

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LDL on cell membranes, and LDL levels are 2–3 times elevated compared to normal subjects [5]. Cholesterol-lowering diets have only a limited effect, which makes treatment with (a combination of) drugs necessary in these patients. A new class of drugs, the cholesterol-synthesis inhibitors, has been used for several years now. These drugs inhibit competitively 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the key enzyme in the biosynthesis of cholesterol. Short-term clinical studies have shown that the cholesterol level can be reduced by means of these drugs by 30–40% on average, with a maximum reduction of 60% of the baseline value, without serious side-effects [6–14]. Furthermore, combination with bile-acid-binding resins can reduce serum cholesterol even further [13].

Simvastatin is the most potent drug in this class [11,14]. After oral ingestion simvastatin is rapidly absorbed by the intestine, reaching its peak plasma concentration after 2 h in healthy volunteers. Approximately 4 h after ingestion the plasma concentrations have fallen by 50%. The main route of excretion is through the biliary tract [for review, see Ref. 15]. Earlier studies of the long-term effects of simvastatin are confined to studies with a mean follow-up of 1.5 years [14]. Simvastatin was introduced as the first drug of this class in our lipid clinic in 1985 for the treatment of patients with familial hypercholesterolaemia. The long-term results of this treatment with a mean duration of 6 years in 55 patients will be discussed.

2. Patients and methods

Patients

In this retrospective study 55 patients with heterozygous familial hypercholesterolaemia were recruited from our out-patient lipid clinic and were treated in the period from 1985 to 1994. The diagnosis of FH was based on patient and family history, lipid profile in the patient and first-degree relatives and the presence of tendon xanthomata. This group consisted of well-characterized FH patients who had participated in earlier short-term studies [6,7]. Lipid-lowering

therapy with simvastatin was started initially in all patients. During treatment 8 patients stopped attending the research program and came under medical supervision elsewhere, 2 patients stopped treatment due to side-effects and 1 patient died of myocardial infarction during treatment. For at least 5 years the remaining 44 patients were treated continuously with simvastatin as monotherapy, or in combination with another lipid-lowering drug. All patients were on a regular cholesterol-lowering diet (cholesterol < 300 mg/day), containing 30% of energy as fat and a 1:1 ratio of saturated and unsaturated fatty acids; they all discontinued any other lipid-lowering drug at least 6 weeks before the start of treatment with simvastatin.

The population consisted of 44 patients, equally divided into 22 men and 22 women. The average age in this population at the start of the study was 44 ± 12 years; the men were on average 11 years younger than the women (Table 1). Out of the 44 patients 14 were overweight (body mass index $> 25.0 \text{ kg/m}^2$). Additional risk factors like hypertension and smoking were found in 5 (11%) and 16 (36%) patients, respectively. One or more vascular complications were diagnosed in 23 patients by means of patient history and physical examination: 16 of 44 (36%) patients had angina pectoris, 4 of 44 (9%) had suffered from a myocardial infarction, 7 of 44 (16%) had peripheral vascular disease (murmur, claudication) and 3 of 44 (7%) had a history of stroke.

Table 1
Demographic characteristics of the study population at baseline ($n = 44$)

	Male ($n = 22$)	Female ($n = 22$)	All patients
Age (years)	39 ± 12	50 ± 9	44 ± 12
BMI (kg/m^2)	24.4 ± 2.5	25.4 ± 4.0	24.9 ± 3.4
Overweight	6 (27%)	8 (36%)	14 (32%)
Cigarette smoking	6 (27%)	10 (45%)	16 (36%)
Hypertension	2 (9%)	3 (14%)	5 (11%)
PVD	3 (14%)	4 (18%)	7 (16%)
Stroke	3 (14%)	0	3 (7%)
CAD	11 (50%)	9 (41%)	20 (45%)

Results represent mean \pm SD; BMI = body mass index; PVD = peripheral vascular disease; CAD = coronary artery disease.

These patients made up the total study population. During treatment of these patients with simvastatin other lipid-lowering drugs were used concomitantly in 30 patients. To be able to deduce the effect of treatment with simvastatin, two groups were selected: (a) patients who had been treated with simvastatin as monotherapy for at least 80% of the period of treatment ($n = 17$), and (b) patients who had been treated with simvastatin and another lipid-lowering drug for at least 80% of the period of treatment ($n = 15$). As additional lipid-lowering drug, cholestyramine was administered in 7 patients, colestipol in 6 patients and gemfibrozil in 2 patients of the second group. The remaining patients did not meet the duration criteria of monotherapy or combination therapy. Treatment with simvastatin varied from 20, 40 to 80 mg/day in the evening, until a maximum cholesterol-lowering effect had been achieved (2 patients received 20 mg/day, 38 received 40 mg/day and 4 patients received 80 mg/day). Initially all patients were examined every 3 months. Subsequently, the intervals were extended from 3 to 6 months. At every examination blood was taken for determination of serum lipids, creatine phosphokinase (CK) and alanine aminotransferase (ALAT) levels.

Analytical methods

Serum cholesterol and triglycerides were determined by enzymatic methods. The high-density lipoprotein (HDL)-cholesterol was determined

after precipitation of other lipoproteins with polyethylene glycol 6000 [16]. LDL-cholesterol was calculated by subtraction [17].

Statistical analysis

Statistical analyses were performed using the "SPSS"-software package for personal computers. For analyses of trends, an analysis of variance (ANOVA) was used, corrected for repeated measurements, and followed by a Mann-Whitney U-test. A two-sided p -value of less than 0.05 was considered to be significant. Unless indicated elsewhere, values are expressed as mean \pm SD.

3. Results

Lipids

The baseline serum cholesterol level of the total population of 44 patients was 11.46 ± 1.68 mmol/l (Table 2). During treatment with simvastatin a reduction in serum cholesterol level of 37.6% was assessed after 0.5 years. After 6 years the decrease in relation to the baseline value was 38.3%. There were no significant differences in the intervening years. A similar pattern was noted for the LDL-cholesterol level, which decreased, compared to the baseline value, by 43.3% after 0.5 years and 44.4% after 6 years. The serum triglycerides also decreased during treatment by an average of 14.0% over the 6-year period (Table 2). During simvastatin treatment the HDL-

Table 2

Serum total cholesterol (Tot.chol), low-density-lipoprotein cholesterol (LDL-C), high-density-lipoprotein cholesterol (HDL-C) and triglycerides (TG) in patients with heterozygous familial hypercholesterolaemia, treated > 5 years with simvastatin alone or in combination with another lipid-lowering drug

	Tot. chol.	%	LDL-C	%	HDL-C	%	TG	%	<i>n</i>
Baseline	11.46(1.68)		9.69(1.64)		1.05(0.26)		1.74(0.69)		44
0.5 year	7.10(1.24)	-37.6 *	5.42(1.19)	-43.3 *	1.15(0.27)	+11.9 *	1.41(0.76)	-18.3 *	44
1.0 year	6.98(1.20)	-38.6	5.17(1.17)	-46.4	1.18(0.32)	+13.6	1.45(0.75)	-14.0	44
2.0 years	6.93(1.13)	-39.1	5.16(1.08)	-46.5	1.20(0.36)	+14.8	1.42(0.62)	-15.0	43
3.0 years	7.11(1.01)	-37.0	5.33(1.05)	-44.2	1.15(0.32)	-10.2	1.56(0.92)	-11.0	44
4.0 years	6.93(0.96)	-38.5	5.13(1.01)	-46.0	1.21(0.29)	+13.7	1.42(0.68)	-15.5	41
5.0 years	7.08(1.03)	-37.4	5.25(1.04)	-44.9	1.22(0.37)	+16.7	1.51(0.76)	-9.9	43
6.0 years	7.01(1.18)	-38.3	5.31(1.07)	-44.4	1.14(0.38)	+9.9	1.35(0.77)	-21.9	34
Mean		-37.8		-45.0		+14.4		-14.0	

Data represent mean (\pm SD) in mmol/l. n = number of patients.

* $p < 0.05$ vs. baseline (ANOVA, Mann-Whitney U-test).

Table 3

Serum total cholesterol (Tot.chol.), low-density-lipoprotein cholesterol (LDL-C), high-density-lipoprotein cholesterol (HDL-C) and triglycerides (TG) in patients with heterozygous familial hypercholesterolaemia, treated > 5 years with simvastatin as monotherapy

	Tot. chol.	%	LDL-C	%	HDL-C	%	TG	%	n
Baseline	11.07(1.51)		9.29(1.51)		1.10(0.36)		1.53(0.61)		17
0.5 year	6.72(1.29)	-38.4 *	5.11(1.27)	-43.8 *	1.25(0.28)	+15.8 *	1.14(0.60)	-26.3 *	17
1.0 year	6.68(0.79)	-39.2	4.84(0.80)	-47.5	1.26(0.28)	+15.7	1.22(0.43)	-17.0	17
2.0 years	6.93(1.20)	-37.5	5.16(1.19)	-44.7	1.29(0.32)	+17.5	1.19(0.45)	-19.8	16
3.0 years	6.81(1.13)	-38.1	5.12(1.24)	-44.8	1.19(0.32)	+15.0	1.23(0.58)	-16.8	17
4.0 years	6.74(1.14)	-37.5	5.00(1.17)	-44.5	1.27(0.25)	+13.8	1.13(0.46)	-22.8	16
5.0 years	6.84(0.87)	-37.4	5.12(0.93)	-43.9	1.22(0.28)	+11.7	1.18(0.61)	-23.0	17
6.0 years	6.91(1.09)	-35.1	5.12(1.01)	-42.1	1.27(0.36)	+17.0	1.22(0.82)	-20.6	13
Mean		-37.7		-44.6		+16.2		-20.5	

Data represent mean (\pm SD) in mmol/l. n = number of patients.

* $p < 0.05$ vs. baseline (ANOVA, Mann-Whitney U-test).

cholesterol level was constantly significantly elevated with values varying from 9.9% after 6.0 years to 16.7% after 5 years, with an overall mean of 14.4% (Table 2).

Before treatment with simvastatin, the serum cholesterol level was severely increased in all patients (varying from 8.24 to 14.78 mmol/l). After 5 years of treatment, 25% of the patients had a cholesterol level of less than 6.4 mmol/l, 50% between 6.4 and 7.8 mmol/l, and 25% of the patients had a serum cholesterol level which was still above 7.4 mmol/l.

From 17 patients who were on monotherapy with simvastatin, the baseline cholesterol level was 11.07 ± 1.51 mmol/l and the LDL-cholesterol level 9.29 ± 1.51 mmol/l (Table 3). The daily dose of simvastatin ranged from 20, 40 to 80 mg

(1 patient received 20 mg/day, 14 received 40 mg/day and 2 patients received 80 mg/day). The baseline values of the total cholesterol and the LDL-cholesterol of 15 patients who received combined therapy were higher than in the monotherapy group (12.31 ± 1.71 mmol/l and 10.55 ± 1.71 mmol/l, respectively) (Table 4). The daily dose of simvastatin was 40 and 80 mg (14 patients received 40 mg/day and 1 patient received 80 mg/day).

During treatment a sustained reduction in serum cholesterol levels was observed. During the course of time there was no change in cholesterol-lowering effect (Figs. 1 and 2). After 6 years of treatment the serum total cholesterol level declined by 35.3% in the patients of the monotherapy group and by 43.6% in the patients

Table 4

Serum total cholesterol (Tot.chol.), low-density-lipoprotein cholesterol (LDL-C), high-density-lipoprotein cholesterol (HDL-C) and triglycerides (TG) in patients with heterozygous familial hypercholesterolaemia, treated > 5 years with simvastatin in combination with another lipid-lowering drug

	Tot. chol.	%	LDL-C	%	HDL-C	%	TG	%	n
Baseline	12.31(1.71)		10.55(1.71)		0.97(0.20)		2.00(0.79)		15
0.5 year	7.85(1.22)	-36.2 *	6.08(1.17)	-42.4 *	1.10(0.21)	+13.4 *	1.72(0.91)	-14.0 *	15
1.0 year	7.03(1.45)	-42.9	5.22(1.48)	-50.5	1.11(0.31)	+14.4	1.72(0.98)	-14.0	15
2.0 years	6.57(1.06)	-46.6	4.83(0.91)	-54.2	1.10(0.28)	+13.4	1.58(0.62)	-21.0	15
3.0 years	6.94(0.68)	-43.6	5.08(0.81)	-51.9	1.13(0.29)	+16.5	1.79(1.14)	-10.5	15
4.0 years	7.06(0.71)	-42.7	5.20(0.81)	-50.7	1.16(0.24)	+19.6	1.66(0.69)	-17.0	14
5.0 years	7.08(1.13)	-42.5	5.16(1.16)	-51.1	1.16(0.29)	+19.6	1.81(0.74)	-9.5	15
6.0 years	6.94(1.33)	-43.6	5.30(1.11)	-49.8	0.96(0.14)	-1.0	1.66(0.80)	-17.0	12
Mean		-42.6		-50.3		+14.0		-12.5	

Data represent mean (\pm SD) in mmol/l. n = number of patients.

* $p < 0.05$ vs. baseline (ANOVA, Mann-Whitney U-test).

Simvastatin monotherapy
(n=17)

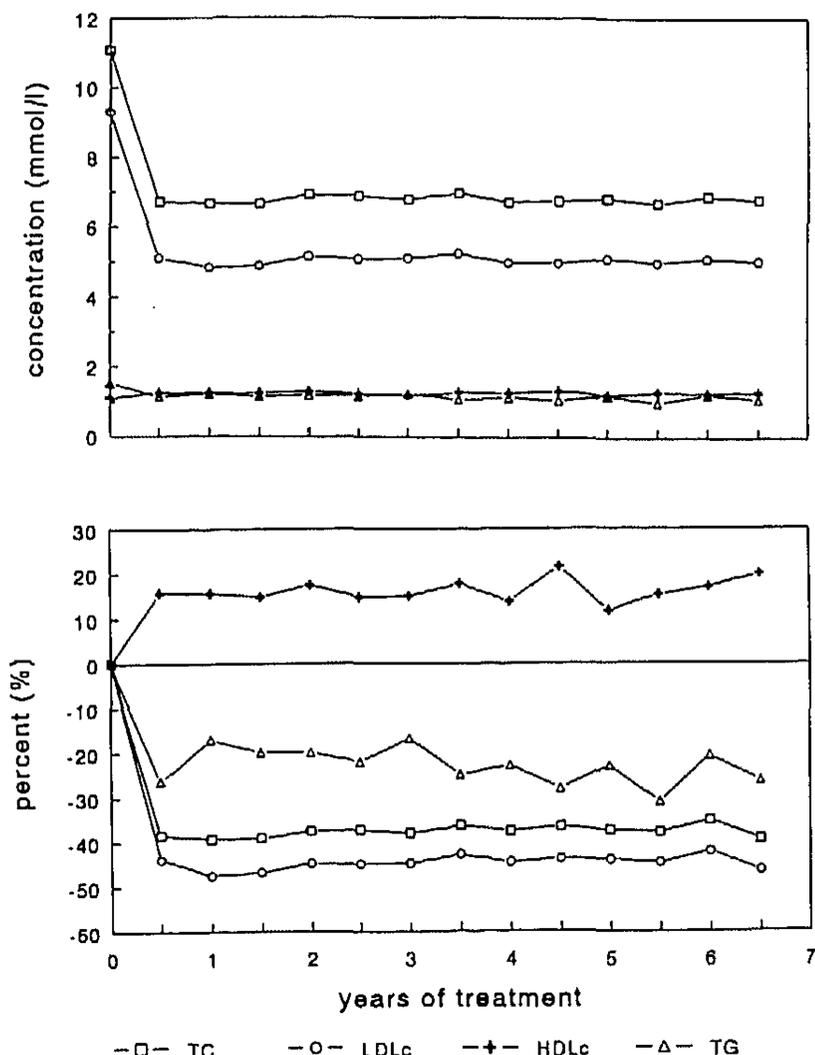


Fig. 1. Mean changes in lipid levels over time in response to long-term simvastatin monotherapy (20-80 mg/day). Top, absolute values; bottom, percent change.

from the combination-therapy group. With respect to the LDL-cholesterol level, these percentages were 42.1 and 49.8, respectively (Tables 3 and 4). In terms of percentages the decrease in serum cholesterol and LDL-cholesterol levels was significantly greater in the combination-therapy group. In the monotherapy group the triglyceride level had significantly declined by a mean of 20.5% over the 6-year period; in the combination-therapy group this decline was significantly lower with an average of 12.5% (Tables 3 and 4). In these two groups a mean increase in HDL-cholesterol was observed of 16.2 and 14.0%, respectively, over the 6-year period.

Clinical events and side-effects

One patient of this group died at age 67 from a myocardial infarction; he was known to have had severe coronary atherosclerosis and had been

using simvastatin for 2 years. Another patient suffered from a myocardial infarction at age 46, and a third one developed angina pectoris at age 43. Both patients used simvastatin for 1 year.

Two patients stopped taking simvastatin medication due to the occurrence of side-effects. One subject, who was on simvastatin for 3 years without problems, stopped taking the drug due to complaints of dizziness, which disappeared after discontinuation and recurred after rechallenge. The other patient complained of insomnia during therapy after several months.

During treatment an elevation of the ALAT concentration occurred in 13 of the total of 44 patients (30%). At one point the ALAT level exceeded the upper level of normal (≤ 30 U/l) by more than 100% in 2 patients. In one patient an increase of more than 200% of the upper limit of normal was measured in the ALAT level. In 11

Combination therapy
(n=15)

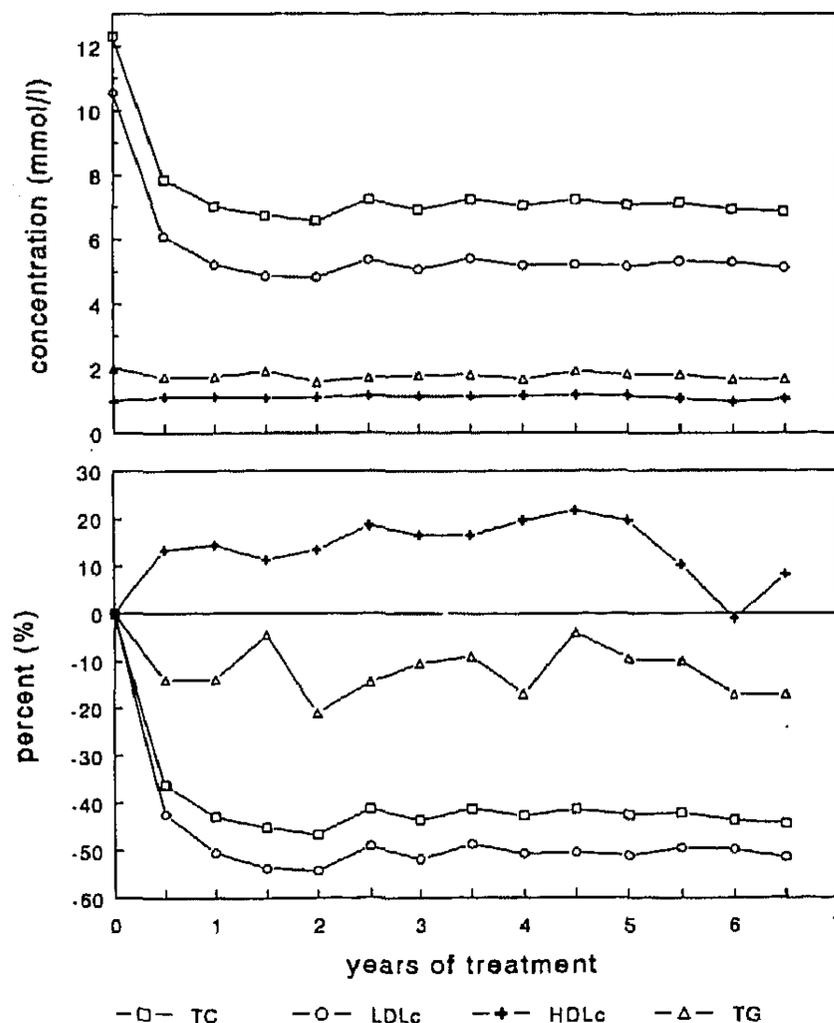


Fig. 2. Mean changes in lipid levels over time in response to long-term combination therapy. Top, absolute values; bottom, percent change.

of the 13 patients the ALAT level returned to normal, although simvastatin treatment was continued. A consistently elevated ALAT level, between 30 and 60 U/l, occurred in 2 patients. The elevation of the ALAT level of one of these 2 patients may have been caused by excessive alcohol consumption. Simvastatin treatment was not interrupted in either of them.

A rise in the CK level above the upper limit of normal (≤ 100 U/l) was measured one or more times in 19 patients (43%). A CK level between 100 and 200 U/l was measured in 8 patients, between 200 and 300 U/l in 9 patients, and 2 patients once had a CK level between 400 and 500 U/l. These levels were not accompanied by muscle complaints. They were usually observed after considerable physical exercise and did not recur at the next examination.

4. Discussion

In this report we present our experience with simvastatin in the treatment of patients with familial hypercholesterolaemia with a follow-up of more than 5 years. The group of patients represented a highly motivated category of subjects with a severely increased risk of coronary events (45% had already had coronary disease at entry to the study, a mean baseline cholesterol level of 11.5 mmol/l, and a family history of coronary disease), which may help to explain the markedly consistent and strong hypolipidaemic effect of treatment. During use of the drug the serum total cholesterol level fell by approximately 38%. The cholesterol-lowering effects especially concerned the LDL-cholesterol level, which decreased by approximately 45%. These decreases are of equal size compared to decreases observed earlier shortly after initiation of the therapy [6,7]. In spite of this considerable lipid-lowering effect of simvastatin, only 25% of the study population reached a total cholesterol level of less than 6.4 mmol/l, as a result of the very high cholesterol baseline values in these patients with heterozygous FH. This makes the administration of a combination of drugs with a different mode of action mostly necessary in this population.

During monotherapy the changes in terms of percentages were not related to the baseline values. There was a decrease in the triglyceride level and a rise in the HDL-cholesterol level, also comparable to those observed in short-term studies [6,7]. In patients who still had an elevated cholesterol level during monotherapy with simvastatin, in spite of a considerable decrease in terms of percentages, the addition of a bile-acid-binding resin resulted in a further decrease in total cholesterol of 5% of the baseline value, but a less marked decrease in serum triglycerides.

During the course of the follow-up only 3 (6.8%) patients suffered from a cardiac event. This figure is comparable to the number of events found in a larger study with lovastatin [10]. Although this event rate may seem low considering the high-risk nature of the study population, our study cannot provide information on reduction of coronary risk, because there was no parallel control group. Several angiographic investigations with surrogate endpoints show less progression of coronary atherosclerosis in actively treated patients with an even lower risk, including the recently reported Multicentre Anti-Atheroma Study, which also applied simvastatin (18). Data from the PLAC-II study suggested a reduction of coronary events after 3 years of treatment with pravastatin, and showed a slowing of the progression of atherosclerosis in the carotid artery [19]. The results of several large trials of the HMG-CoA reductase inhibitors have to be awaited considering the possibly greater prevention potential in comparison to older drugs like resins, fibrates and niacin.

The effects of cholesterol synthesis inhibitors are not limited to patients with familial hypercholesterolaemia. These drugs are also very effective with other forms of hypercholesterolaemia, including familial combined hyperlipidaemia, familial dysbetalipoproteinaemia, and secondary forms of hypercholesterolaemia [20,21].

The inclusion of a control group would have made the interpretation of adverse events easier, but this was of course impossible in this group of FH patients in such a lengthy study. Subjective side-effects, however, hardly occurred and led to discontinuation of treatment in just 2 patients. In

general, the cholesterol synthesis inhibitors are well tolerated. Subjective adverse experiences reported are limited to abdominal pain, flatulence, constipation, and headache, each occurring in 1–3% of patients, and they appear not to differ from those caused by the most widely used drugs (lovastatin, simvastatin, pravastatin) [for review, see Ref. 21].

Concern about possible induction of lens opacities in the early years of use of cholesterol synthesis inhibitors has not been realized, and regular ophthalmological examinations are no longer required [14,21].

A small percentage of patients complain about central nervous system effects, such as headache and insomnia, during treatment with cholesterol synthesis inhibitors [22,23]. A causal relationship between the cholesterol synthesis inhibitors and these adverse effects remains unclear because of the high prevalence of these symptoms in untreated patients. The EXCEL study of lovastatin including over 8000 patients showed no significant excess of headache (2.6–3.2% in the active-drug-treated patients) over that in the placebo group (2.7%) [22].

Transaminase elevations have been reported in virtually all clinical trials of this class of drugs. In EXCEL, the percentage of patients with an elevation of transaminases above 3 times the upper limit of normal increased dose-dependently from 0.1% on placebo and 20 mg/day to 1.5% on 80 mg/day [22]. In the 1.5-year follow-up study of simvastatin in 2400 patients taking 20–40 mg/day, 1% developed increases of transaminases of more than 3 times the upper normal level [14]. Currently, we recommend that liver function tests be monitored every 6 weeks in the first 6 months and periodically thereafter (2 times per year), and to stop the drug if transaminases increase above 3 times the upper limit of normal [21].

CK elevations can result from exercise or minor muscle trauma and are often not drug-related; in EXCEL, 29–35% of patients on active drug had CK elevations at some time during the study, but this was also present in 29% of patients on placebo [22]. Muscle symptoms developed in 7–9% of patients both on placebo and on effective drug. Frank myopathy was observed in 5

out of 6582 patients receiving active drug (0.08%), but no rhabdomyolysis developed. In the 1.5-year study of simvastatin, myopathy was observed in 0.08% of 2400 patients [14]. Rhabdomyolysis has been reported with HMG-CoA reductase inhibitors used in combination with gemfibrozil, cyclosporin, erythromycin or nicotinic acid [21]. Currently, it appears not to be useful to monitor CK levels in order to reveal myopathy; patients should be instructed to contact their physician when muscle symptoms occur.

In conclusion, the efficacy of simvastatin was fully maintained during this long-term follow-up, with good tolerability and a low adverse event rate. Undoubtedly, this class of drugs will prove to have a great impact on both total and cardiovascular morbidity and mortality in this high-risk patient group.

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