A comparison of the effects of simvastatin and pravastatin monotherapy on muscle histology and permeability in hypercholesterolaemic patients

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1 In this double-blind, placebo controlled, prospective study, it was assessed whether simvastatin or pravastatin monotherapy have adverse effects on muscle histology and muscle membrane permeability in hypercholesterolaemic patients.

2 Twenty-four patients, seven females and 17 males, with primary hypercholesterolaemia (LDL cholesterol levels ≥ 4.14 mmol l^{-1}) were selected from the outpatient lipid clinic of a 650 bed academic medical centre.

3 After a 6-week lipid lowering diet and placebo period, patients were randomized into two groups of 12 subjects with similar characteristics, to receive either simvastatin or pravastatin in dosages of 10–40 mg day^{-1} for three periods of 6 weeks. After each 3-week period the dose was adjusted to LDL cholesterol to aim for equipotent dosage.

4 All subjects performed a 45 min, lean body mass standardized bicycle ergometer test, before and after 18 weeks of treatment. As parameter for muscle damage, the exercise-induced rise of the muscle proteins, creatine kinase (CK) and myoglobin (Mb), relative to pre-exercise levels, were determined 1 and 8 h after the test. Forty-eight hours after each test a biopsy was taken from the quadriceps muscle and histology was judged by three independent observers.

5 Eighteen weeks of monotherapy with simvastatin and pravastatin did not affect the exercise induced release of CK and Mb, neither were any differences observed in muscle histology before and after treatment with either of the drugs.

6 Although simvastatin doses were lower than pravastatin, reductions in total- and LDL-cholesterol were greater in the simvastatin treated patients than in the pravastatin treated group.

7 We conclude that no evidence is found for muscle damage after 18 weeks of monotherapy with equipotent doses of either simvastatin or pravastatin.

Keywords hypercholesterolaemia simvastatin pravastatin myopathy creatine kinase myoglobin exercise muscle biopsy

Introduction

Inhibitors of the rate limiting enzyme in the cholesterol-synthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, have gained an important place in the treatment of hypercholesterolaemia. Although these drugs have been proven relatively safe so far, adverse effects on skeletal muscles have been described, ranging from asymptomatic elevations of serum creatine kinase (CK) to severe rhabdomyolysis: Lovastatin is associated with elevations of CK serum levels without symptoms in 11% of the patients [1]. These CK elevations seem to be dose related and associated with physical exercise [1, 2]. Myopathy, defined as muscle tenderness combined with CK levels elevated more than 10 times the upper limit of normal (ULN), is reported in 0.1 to 0.2 percent of the patients treated with lovastatin [2–5].

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When lovastatin is combined with gemfibrozil, the incidence of myopathy is 5–30% [6–9]. Rhabdomyolysis has been reported in combinations of lovastatin with erythromycin, niacin or cyclosporin [3, 10–13]. Simvastatin, a more powerful HMG-CoA reductase inhibitor than lovastatin, is associated with elevations of CK and myopathy as well [14–17]. Pravastatin, which has been claimed to cause less adverse reactions due to its hydrophylicity, has nevertheless also been associated with elevations of CK and myopathy [18, 19]. Since treatment with these drugs should be continued lifelong, it is important to study the relation between HMG-CoA reductase inhibitors and muscle pathology and to see whether there are differences between two statins which differ in water/lipid solubility. In this study, muscle damage is determined by assessing the release of the muscle proteins CK and myoglobin (Mb) following a lean body mass (LBM) standardized exercise provocation test in 24 hypercholesterolaemic patients before and during treatment with simvastatin or pravastatin. This test is based on the fact that the exercise induced release of CK and Mb is more pronounced in subjects with (subclinical) muscular pathology than in normals [20–23]. Furthermore, muscle biopsies to detect histologic alterations under HMG-CoA reductase inhibition are obtained.

Methods

Patients

Twenty-four patients with primary hypercholesterolaemia, 17 men and seven women, age 51 ± 8 years, having low-density lipoprotein (LDL) cholesterol levels ≥ 4.65 mmol l^{-1} and triglycerides (TG) < 4.6 mmol l^{-1}, were selected from recently diagnosed hypercholesterolaemic patients from the Lipid Clinic of the University Hospital Utrecht. Patients with diabetes mellitus, renal, hepatic, muscle or cardiac diseases were excluded. Diseases or drug-therapy, known to be accompanied with elevated CK or Mb levels were excluded as well. Before entering the study, informed consent was obtained from all patients.

Study protocol

The study protocol was approved by the Medical Ethics Committee of the University Hospital Utrecht. The patients entered a dietary baseline period of 6 weeks. They were instructed by a dietician and consumed a standard lipid lowering diet containing 50% of calories from carbohydrates, 20% from proteins, 30% from fat with a polyunsaturated-/saturated lipid ratio of 1. Daily intake of cholesterol was <300 mg. During this 6-week period, the patients received two placebo-tablets each evening; one resembling simvastatin 10 mg, the other resembling pravastatin 10 mg. At the end of the 6-week baseline period, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and TG levels were determined. LDL

cholesterol was calculated using the Friedewald formula [24]. Patients with LDL cholesterol ≥ 4.14 mmol l^{-1} were randomized into two treatment groups; one to be treated with simvastatin, the other to be treated with pravastatin. The active treatment phase consisted of three successive periods of 6 weeks. At the end of each period, fasting lipid levels and safety parameters were measured. Patients were interviewed for tolerability and adverse events. A physical examination was performed after each treatment period. Dietary adherence was evaluated and a tablet count was performed to assess drug compliance. The attainment of an equipotent dosage regime of simvastatin or pravastatin was attempted in the following manner. In the simvastatin treatment group, patients were treated with 10 mg simvastatin in the ever.ing and pravastatin placebo. In the pravastatin group, patients started with 10 mg pravastatin in the evening and simvastatin placebo. If at the end of the first 6-week treatment period LDL cholesterol was ≥ 3.4 mmol l^{-1}, active medication doses (simvastatin or pravastatin) and placebo were doubled to 20 mg day^{-1}. Using the same criterion after 12 weeks of treatment, active medication and placebo were doubled again, to a maximum of 40 mg day^{-1}. If LDL cholesterol was <2.6 mmol l^{-1} after 6 or 12 weeks of treatment, doses of active medication and placebo were halved to a minimum dosage of 10 mg simvastatin or pravastatin/day.

Myopathy assessment

Ergometer test   In the last week of the dietary baseline period and after 18 weeks of active treatment, an exercise provocation test was performed. The test was used before to detect carriers of Duchenne's muscular dystrophia [22, 23]. This is a 45 min long exercise-performance test on a bicycle ergometer, load 2 watt kg^{-1} lean body mass (total body weight minus body fat content). Body fat content was estimated by measurement of biceps-, triceps-, subscapular- and suprapelvic skin folds. Heart frequency was registered very 5 min and kept below the value calculated by 220 minus age in years. Work load was registered every 5 min and reduced if necessary. During the second exercise test (in the last week of the active treatment period), work load was kept identical to the work load during the first test for each individual. The patients were told to avoid strenuous exercise during 24 h before the test. Blood samples for CK and Mb analysis were taken before the exercise test as well as 1 and 8 h after the test. It was demonstrated before that peak CK levels occur 8 h after the test whereas peak Mb are observed 1 h after exercise [20–23, 25]. The exercise induced muscle damage is reflected by the maximal rise in CK and Mb levels after exercise (i.e. the difference between post-exercise peak CK and Mb levels and pre-exercise levels) [20, 22, 23, 25].

Muscle biopsy   Forty-eight hours after both exercise tests, the patients underwent a muscle biopsy. After local anaesthesia with Marcaine® 0.5%, a disposable

biopsy needle (Travenol Tru-Cut®, 14 Ga, 15.2 cm cannula, 20 mm specimen notch) was introduced in the musculus quadriceps femoris, vastus lateralis, about 10 cm proximal of the upper patella margin [26]. This site was chosen, because in statin related myopathy proximal muscles are affected. Myotoxic effects during treatment with HMG-CoA reductase inhibitors are mostly seen in type 2 muscle fibres. The quadriceps muscle contains all types of muscle fibres (1, 2a and 2b) in equal amounts and distributed equally [27]. Moreover, exercise load is heaviest in the quadriceps muscle. After biopsy, an elastic bandage was applied for 12 h. The biopsies were embedded in Lipshaw Embedding Medium® and frozen in isopentane cooled with liquid nitrogen. They were kept at −75° C. Muscle biopsy sections were stained with haematoxylin and eosin. Biopsies in random order were studied by three independent observers, who were blind to treatment modality. They classified the biopsies as 'normal, abnormal or indeterminable'. The final classification was the one given by at least two of the three observers. A preparation was classified 'abnormal' when there were signs of white-blood-cell infiltration, phagocytosis in the muscle tissue or hypercontraction of muscle fibres. When the amount of muscle tissue in the section was too small or there were too many artifacts to give proper judgment, the classification 'indeterminable' was given. From a number of patients, two sections from the same biopsy specimen, were presented to the observers. When the classification of these two biopsies differed (e.g. one 'normal' and one 'abnormal') the ultimate classification was 'indeterminable'.

Laboratory methods Plasma lipid levels were measured in plasma portions taken after 12 h overnight fasting. TC and TG levels were determined by enzymatic-colorimetric methods (Boehringer Mannheim CHOD-PAP and GPO-PAP®). HDL cholesterol was determined in the supernatant after precipitation of LDL and very low density (VLDL) cholesterol. Mb

was assessed using the Behring Nephelometer® and the Behring NA Latex Myoglobin Kit®. Samples from each subject were measured in duplicate in the same assay run.

Statistical methods All values in this study are presented as mean ± standard deviation. Student's *t*-test was used to analyze lipid levels within and between the two treatment groups and to compare mean drug dosage, lean body mass and exercise load between the two groups. Pre-exercise CK and Mb levels as well as the exercise induced rise in CK and Mb were compared between the first exercise test (without treatment) and the second exercise test (during treatment) within both of the treatment groups using the Wilcoxon test for paired measures. Pre-exercise levels of CK and Mb and post-exercise rise of these proteins were compared between the simvastatin and pravastatin group for both of the exercise tests using the Mann-Whitney test. Chi-square testing was performed to compare gender between the two groups and to compare the qualifications of the muscle biopsies taken after the first and second exercise tests within and between both treatment groups. Inter-observer consistency in muscle biopsy observers was analysed by k-statistics [28]. In all tests a *P* value of less than 0.05 was considered significant.

Results

Two patients could not be analysed of the 24 patients who entered the study. One patient in the simvastatin group could not perform the second ergometer test because of angina pectoris, the other patient discontinued the study for personal reasons, unrelated to the drug used. The pravastatin and simvastatin treatment groups at the end of the baseline period were identical with regards to age, gender and lipid parameters (Table 1). Results of the first exercise test, before

Table 1 Similar characteristics of the simvastatin and pravastatin treatment groups at the end of the baseline period (values expressed as mean ± s.d.)

	Simvastatin group	*Pravastatin group*
Number of patients	12	12
Sex (males/females)	7/4	9/2*
Mean age (years)	49.6 ± 7.6	54.4 ± 9.3[†]
Total cholesterol (mmol l⁻¹)	7.84 ± 0.87	7.92 ± 1.08[†]
LDL-cholesterol (mmol l⁻¹)	6.00 ± 0.85	6.06 ± 1.13[†]
HDL-cholesterol (mmol l⁻¹)	1.10 ± 0.27	1.15 ± 0.12[†]
Triglycerides (mmol l⁻¹)	1.66 ± 0.59	1.50 ± 0.20[†]
Ergometer test		
Lean body mass (LBM, kg)	51.0 ± 8.2	54.0 ± 8.8[†]
Mean workload		
(watt kg⁻¹ LBM)	1.9 ± 0.2	21. ± 0.3[†]

*$P > 0.05$, Chi-square test.
[†]$P > 0.05$, Student's *t*-test.

treatment, did not differ with regards to lean body mass, workload (Table 1), absolute pre-exercise CK and Mb levels, rise of CK and Mb levels, 1 and 8 h after the first exercise test (Table 3) and muscle histology (Table 4). Therefore both treatment groups had similar characteristics before treatment was started. Because dosage was dependent on serum LDL cholesterol levels at 6 and 12 weeks of treatment, patients within one treatment group (simvastatin or pravastatin) received different doses of active medication (Table 2). Mean dosages of active medication per patient, however, did not differ between the two groups.

Lipid parameters

Lipid concentrations at the end of the baseline period and the end of the last 6-week treatment periods are given in Table 2. In both groups, significant reductions in TC and LDL cholesterol compared with baseline levels were achieved; 30.4% and 44.5% respectively, for the simvastatin group, 21.0% and 33.7% for the pravastatin group. HDL cholesterol levels at the end of the third treatment period rose by 17.3% in the simvastatin and 22.6% in the pravastatin group. TG levels did not differ from baseline levels in both groups. TC and LDL cholesterol levels at the end of the third treatment period differed between the two treatment groups: simvastatin therapy resulted in greater reductions in LDL cholesterol than pravastatin therapy.

Myopathy assessment

Exercise provocation test The two treatment groups did not differ in lean body mass and mean workload (Table 1). All patients had the same workload at any point of time during the second exercise test as during the first one. Pre-exercise absolute CK and Mb

levels and exercise induced rise in CK and Mb, determined 1 and 8 h after exercise, are given in Table 3. Maximal rises in CK and Mb were observed 8 resp 1 h after all tests. Absolute pre-exercise CK levels did not differ between the baseline exercise test and the second exercise test within either of the treatment groups, neither did the rise in CK levels, 1 and 8 h after exercise. Three subjects (nos 3, 4 and 7) in the simvastatin and one subject (no. 9) in the pravastatin group had elevated pre-exercise CK levels before the first test. CK levels before the second exercise test were elevated in these subjects as well, except in no. 3 of the simvastatin group. It was verified that these subjects had not experienced physical exercise before both tests. No differences in pre-exercise Mb levels between the first and second exercise test were observed, within both of the treatment groups and the same was true for the post-exercise rise in Mb levels, 1 and 8 h after exercise. Subject 5 in the simvastatin group had an impressive rise in Mb after the first exercise test. Leaving out subjects 3 and 5 in the simvastatin group did not induce differences between first and second exercise test. No differences between the simvastatin and pravastatin group were observed in pre-exercise CK and Mb levels and post-exercise rise of these proteins for both of the exercise tests.

Muscle biopsies Muscle biopsy was not successful in two patients at the end of the baseline period, one in the simvastatin and one in the pravastatin treatment groups. The results of the other muscle biopsies are given in Table 4. Agreement between the observers was fair to moderate/substantial [28]. No differences in muscle histology were found, between the two series of biopsies, within either treatment group and between the two groups for both tests. Three muscle biopsies at the end of the placebo period and four after active treatment were classified

Table 2 Lipid parameters in two groups of 11 hypercholesterolaemic patients before and during treatment with equipotent doses of simvastatin or pravastatin (all values expressed as mean ± s.d., lipids in mmol l^{-1}, dose in mg)

		Time (weeks)			Percentual decrease vs baseline
	Baseline	6	12	18	
Simvastatin					
TC	7.84 ± 0.87	5.77 ± 0.74	5.77 ± 0.97	5.46 ± 0.60	(−30.4)*[†]
LDL	6.00 ± 0.85	3.81 ± 0.86	3.52 ± 0.77	3.33 ± 0.49	(−44.5)*[†]
HDL	1.10 ± 0.27	1.12 ± 0.30	1.20 ± 0.34	1.29 ± 0.28	(+17.3)*
TG	1.66 ± 0.59	1.72 ± 0.82	1.71 ± 0.97	1.83 ± 0.89	(+10.3)
dose of drug	0.00 ± 0.00	10.00 ± 0.00[‡]	17.27 ± 4.45[‡]	28.28 ± 11.13[‡]	
Pravastatin					
TC	7.92 ± 1.08	6.21 ± 0.66	6.23 ± 0.77	6.26 ± 0.74	(−21.0)*
LDL	6.06 ± 1.13	4.55 ± 1.00	4.30 ± 0.83	4.02 ± 0.85	(−33.7)*
HDL	1.15 ± 0.12	1.13 ± 0.22	1.27 ± 0.16	1.41 ± 0.25	(+22.6)*
TG	1.50 ± 0.20	1.18 ± 0.85	1.45 ± 0.72	1.85 ± 1.18	(+23.3)
dose of drug	0.00 ± 0.00	10.00 ± 0.00	19.09 ± 2.87	35.45 ± 9.88	

*$P < 0.001$ vs baseline value, Student's t-test.
[†]$P < 0.01$ vs pravastatin group, t-test.
[‡]$P > 0.05$ vs pravastatin group, t-test.

Table 3 Rise of serum creatine kinase (CK) and myoglobin (Mb), 1 and 8 h after standardized exercise compared with baseline levels in two groups of 11 hypercholesterolaemic patients. The first exercise test was performed before treatment, the second test after 18 weeks of treatment with simvastatin or pravastatin

		CK $(u$ $l^{-1})$	Rise		Mb $(ng$ $dl^{-1})$	Rise		CK $(u$ $l^{-1})$	Rise		Mb $(ng$ $dl^{-1})$	Rise		End dosage
	Time (h)													
Patient	Gender	0	1	8	0	1	8	0	1	8	0	1	8	$(mg$ $day^{-1})$
Simvastatin														
1	m	70	3	15	42	2	-13	75	3	3	47	5	6	40
2	m	74	8	5	26	3	-6	51	4	11	33	0	-4	40
3	m	184	11	165	76	33	-9	98	15	99	34	22	5	40
4	m	180	17	14	22	22	6	263	-20	20	32	21	20	40
5	m	63	37	119	32	213	3	54	23	48	26	83	7	20
6	m	44	11	33	21	23	31	53	24	19	30	6	7	20
7	m	126	0	10	40	4	11	108	0	29	32	7	9	10
8	f	39	3	27	18	14	3	52	5	15	28	-7	-11	40
9	f	64	6	20	33	3	-6	48	3	-22	55	19	-22	20
10	f	83	5	32	33	16	20	58	3	18	32	22	7	20
11	f	52	2	-3	24	4	-	41	5	20	32	-1	-3*	20
Mean		89.0†‡	9.4†‡	39.7†‡	33.4†‡	30.6†‡	4.0†‡	81.9‡	4.1‡	27.5‡	34.6‡	16.1‡	1.9‡	28.2
s.d.		49.1	9.9	50.3	15.4	58.5	13.0	60.8	9.9	25.0	8.2	23.3	10.8	11.1
Pravastatin														
1	m	34	0	51	26	-4	2	31	3	9	26	45	32	40
2	m	41	1	9	25	4	-1	54	-4	9	39	1	-3	40
3	m	52	0	3	24	3	-3	98	-2	-13	30	3	-4	40
4	m	45	9	11	34	2	-4	39	5	34	26	11	14	40
5	m	88	-2	7	20	7	2	87	-7	4	37	36	10	40
6	m	71	6	66	30	21	-	84	10	18	37	12	-5*	40
7	m	80	1	-2	28	-1	-	80	2	15	27	6	2*	40
8	m	79	10	15	50	-1	-30	84	7	-1	41	15	-5	20
9	m	136	12	20	21	12	6	303	-9	-21	36	13	-2	10
10	f	46	4	36	30	12	0	48	13	102	36	55	20	40
11	f	31	7	11	14	2	2	42	1	16	24	-1	4	40
Mean		63.9†	4.4†	20.6†	27.5†	5.2†	-2.9†	86.4	1.7	15.6	32.6	17.8	5.7	35.5
s.d.		29.6	4.5	20.4	8.9	7.0	10.0	71.9	6.6	30.8	5.8	18.0	11.5	9.9

*Values not included in calculations because of missing corresponding values.
†$P > 0.05$ vs corresponding values during active treatment, Wilcoxon test.
‡$P > 0.05$ vs corresponding values in pravastatin group, Mann-Whitney test.

'abnormal' in the pravastatin group. No patient had an abnormal histology after placebo and one after active treatment in the simvastatin group. There was no relation between absolute pre-exercise levels of CK or Mb or rise of muscle proteins after exercise and histologic classification.

Discussion

The goal of this study was to determine the relation between monotherapy with the HMG-CoA reductase inhibitors simvastatin and pravastatin and muscle pathology. Reust *et al.* studied CK levels after exercise in healthy volunteers on lovastatin and placebo and did not find any differences between the two groups [29]. In this study, we determined not only CK but Mb as well, since Mb is a more sensitive parameter for muscular pathology after exercise than CK [22, 23, 25, 30]. No differences between pre-exercise absolute CK and Mb and CK and Mb rises were found between the first and second exercise within both groups and between the simvastatin and pravastatin group. Taken the number of subjects par-

ticipating in this study, the observed standard deviations in the exercise induced rise between first and second exercise test and a power of 0.8, it could be calculated that the differences in maximal CK rise (observed 8 h after exercise) between first and second exercise tests had to be 35 u l^{-1} for the simvastatin group and 38 u l^{-1} for the pravastatin group to reach significance. For Mb rise, 1 h after exercise, these levels were 45 ng dl^{-1} for the simvastatin group and 22 ng dl^{-1} for the pravastatin group. In studies on exercise induced muscle protein rise in subjects with subclinical muscle disease, differences in CK and Mb rise between subjects and healthy controls were observed beyond these significance thresholds, and although the pathogenesis of these diseases might differ from statin related myopathy, the number of subjects participating in the present study is sufficient to detect differences in CK and Mb rise that even fall below the values found in other diseases [2–5, 20, 21, 23]. It is striking that absolute pre-exercise CK levels before the first exercise test were elevated in some subjects. This could not be attributed to factors known to be accompanied by elevations of CK. One could wonder if hypercholesterolaemia in itself is associated with muscle damage [31]. We con-

Table 4 Final classification of muscle biopsies, taken 48 h after standardized exercise in two groups of 11 hypercholesterolaemic patients. The first biopsy was taken after the first exercise test at the end of the placebo period, the second one was taken after the second exercise test, during treatment with simvastatin or pravastatin

	Simvastatin			Pravastatin	
Patient	First biopsy	Second biopsy	Patient	First biopsy	Second biopsy
1	N	N	1	I	N
2	N	N	2	I	N
	>N²	>N	3	–	N
2	N	N	4	N	N
3		N	5	N	
	N	>N		>N	N
3		N	5	N	
4		N	6	A	A
	N	>I	7	A	A
4		A	8	A	N
5	N	N	9	A	
6		N		>I	N
	N	>N	9	N	
6		N	10	I	A
7	I	I	11	N	A
8	–	N		>N	
9	I	N	11	N	
10	I	N			
11	I	N			

The number of abnormal muscle biopsies did not differ between both of the series within both of the treatment groups, nor did it differ between the treatment groups for each series (Chi-square test, $P > 0.05$, 2 degrees of freedom).
N = normal   A = abnormal   I = indeterminable.
1 Final classification was the classification given by at least two of the three independent, blind observers.
2 Two samples were presented to the observers. If the final classification was not the same (e.g. one normal, one abnormal), the ultimate classification was 'indeterminable'.

clude that 18 weeks treatment with simvastatin and pravastatin does not influence the exercise induced release of Mb and CK. However, inter-individual differences in response to exercise are substantial and we cannot exclude that certain individuals are more sensitive to the effects of exercise than others [29]. Muscle biopsies were performed to assess the influence of exercise on histology, both under placebo conditions and under treatment with simvastatin or pravastatin. Although the yield of the needle biopsy technique might be less than that of the open muscle biopsy technique, the latter one is far more damaging and burdensome for the patient. Analysis of the results gave no evidence of tissue damage attributable to treatment with HMG-CoA reductase inhibitors. We have no explanation for the abnormal biopsies in three subjects before treatment with pravastatin. These patients did neither experience abnormal baseline muscle protein levels, nor pronounced exercise induced CK or Mb levels. There was no relation between the classifications of the biopsies in both groups and the muscle protein levels after the exercise tests. The possibility remains that if the biopsies had been taken at another point in time after the exercise test or from another muscle the results could have been different. It seems however very unlikely that muscular pathology after exercise would subside within 48 h or would be better detectable even later. Neither in the exercise induced release of CK and Mb, nor in histology did we find indications for statin induced muscle pathology. In young rats simvastatin but not pravastatin treatment results in myopathy and growth retardation [32]. Maybe susceptibility to statin induced myopathy is dependent on developmental stage. In adult humans treated with statins, CK elevations are reported but it is not clear if these are statin-related or pre-existent [31]. Apparently additional factors, interfering with statin metabolism and thereby increasing their systemic levels, are needed to elicit myopathy [3, 10–13, 33]. One could expect differences between pravastatin and simvastatin in adverse systemic effects, due to the fact that pravastatin is hydrophilic and simvastatin is not [18, 33]. These characteristics however were determined *in vitro* only and in assessing systemic adverse effects the influences of drug metabolism have to be taken into account: e.g. the hepatic extraction ratio of simvastatin is larger than that of pravastatin and metabolites of both drugs might or might not have systemic effects as well [35–38]. Indeed, it would be interesting to determine bound and unbound plasma levels of these drugs. The lipid lowering effects of the two drugs are in agreement with the literature [18, 35, 39]. In conclusion, we did not find evidence for muscular pathology after short-term (18 weeks) treatment with the HMG-CoA reductase inhibitors simvastatin or pravastatin, neither by studying the exercise induced release of CK and Mb, nor by histologic examination of muscle biopsies. The question whether long term treatment with HMG-CoA reductase inhibitors might reveal evidence for muscle damage remains to be studied.

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