Title: Pilot study of safety and efficacy of polyprenols in combination with coenzyme Q10 in patients with statin-induced myopathy

Article Type: Original Article/Research

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Abstract: Background and objectives: Statin-induced myopathy (SIM) has been partially attributed to deficiency of dolichol and Coenzyme-Q10 (CoQ10). We tested the safety and efficacy of plant polyprenols in combination with CoQ10 for alleviation of SIM.
Material and methods: In an open-label, one-center prospective pilot study patients with SIM received conifer-tree needle polyprenols (4mg/day) and CoQ10 (100mg/day) for 8 weeks. Symptoms and safety were evaluated according to symptom severity score (0-10), creatine kinase (CK) levels, exercise test, dynamometry, complete blood count, clinical biochemistry and electrocardiography.
Results: Of 14 patients 11 completed the study per protocol. Two patients withdrew consent due to travels abroad, and it was discontinued for one patient with stage 3 chronic kidney disease due to asymptomatic elevations of liver enzymes at week 4. No safety parameters changed significantly in per protocol group. Non-significant increase of CK levels was observed (p=0.231). Muscle pain (n=10) and weakness (n=7) scores improved significantly (p<0.001 and p=0.018, respectively). Muscle pain completely disappeared in 2 patients, weakness completely resolved in 3 patients and cramps disappeared in two patients. Four patients assessed improvement strong enough to consider increase of statin dose. No significant changes were observed in exercise test or dynamometry.
Conclusions: Conifer-tree polyprenols in combination with CoQ10 may be generally safe in patients with SIM, but caution should be exercised in patients with glomerular filtration rate <60 ml/min and routine monitoring of the liver enzymes and CK is advocated in all patients. The observed efficacy provides the rational for larger, double-blind controlled study with polyprenols.

Cover Letter

October 23, 2015

Dear Professor Edgaras Stankevicius,

On behalf of all co-authors I would like to submit an original article for publication in the *Medicina*. The manuscript titled "*Pilot study of safety and efficacy of polyprenols in combination with coenzyme Q10 in patients with statin-induced myopathy*" consists of 32 double-spaced pages including 15 references, five tables and three figures.

To the best of our knowledge no previous study has been published in internationally indexed literature on safety and efficacy of conifer-tree polyprenols in patients with statin-induced myopathy (SIM). There is an unmet need in clinical practice to alleviate symptoms in patients with SIM symptoms. The available options usually envolve decrease of statin dose which leads to an increased cardiovascular risk of these patients.

In this pilot study we investigated a potential role of supplementation with polyprenols in combination with ubiquinone (also known as Coenzyme Q10) to alleviate SIM symptoms, with a special focus on safety. The first experience in SIM patients encourages us to continue the research and to plan a double-blind placebo-controlled prospective study. Based on the current data, the safety alert of a potential hepatotoxicity of the combination may be considered.

I would like to assure you that the results of this study have never been published in the indexed literature nor are currently under reviewing process in any other journal. I would like to confirm that all authors have read and approved the manuscript. I would like to mention that two of the authors have a conflict of interest as the are employees of the sponsor. They took part in the study planning, but not during the execution of the study, which was performed according to the Good Clinical Parctice requirements.

We hope this study would be found as valuable to the journal reviewers.

Sincerely yours,

Gustavs Latkovskis, MD, PhD, associate professor

Clinical and interventional cardiologist

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Conflict of interest statement

Ilona Vanaga and Ugis Kletnieks are employees of Pharma competence center and "Silv EXPO" Ltd.

Pilot study of safety and efficacy of polyprenols in combination with coenzyme Q10 in patients with statin-induced myopathy

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1. Introduction

Treatment with statins is the cornerstone of primary and secondary cardiovascular disease prevention. [1,2] Statins are generally well tolerated, but myopathic symptoms known as statin induced myopathy (SIM) may preclude their administration. The manifestations may vary from subjective symptoms such as muscle pain, weakness and cramps to increased plasma creatine kinase (CK) levels. The most serious adverse muscle side effect, rhabdomyolysis, however is very rare: 1 in 10 000 patient years. [3] So-called statin associated muscle symptoms such as muscle pain, aching, stiffness, weakness or cramps are encountered more frequently (7-29%), in many cases without significant increase in plasma CK levels. [3,4] Although these symptoms are mostly not life threatening, they may lead to down-titration of the dose or discontinuation of statins in up to 75% of cases, which contributes to increased adverse cardiovascular outcomes. [3,5-7]

Objective assessment of muscle side effects remains a challenge. Currently no unified recommendations to enhance accurate diagnosis and approve statin associated muscle symptoms or treatment approach are generally accepted. The common practice in case of suspicion of statin induced muscle side effects is to down-titrate the statin dose, switch to a different statin or discontinue the treatment. [3] Alternatively, etiopathogenic treatment of SIM can be considered. Statins are known to inhibit synthesis of several biologically active substances, including ubiquinone and dolichols, which have been related to SIM. [8] Supplementation with ubiquinone also known as Conenzyme-Q10 (CoQ10) has been used in clinical practice. There was no

evidence, however, of its efficacy in a meta-analysis of six trials including 302 patients and in a randomized trial with 120 patients. [9,10]

Polyprenols are natural long-chain isoprenoid alcohols with chemical formula $H\text{-}[CH_2\text{-}C(CH_3)\text{=}CH\text{-}CH_2]_n\text{-}OH$ with n standing for the number of isoprene units. They are naturally present in conifer tree needles in small amounts and are known to be metabolized in human liver to dolichol which is an important bioregulator of N-glycoprotein synthesis. [11]

We therefore hypothesized that supplementation with polyprenols in combination with CoQ10 could reduce statin induced muscle symptoms and improve objective myopathy parameters.

2. Material and methods

2.1. Study design and patients.

This was an open-label, one-center prospective pilot study. Between June 2014 and July 2015 patients at the Latvian Center of Cardiology were screened for suspected SIM symptoms. The study was approved by the local Committee of Ethics at the Paul Stradins Clinical Hospital (study protocol No.160414 – 3L) and performed according to good clinical practice.

The inclusion criteria were as follows: (i) presence of at least one of symptoms associated with statin use (muscle pain or muscle weakness, or muscle cramps for at least 2 weeks, or elevated CK level >2x and <10x above upper limit of reference (ULR); (ii) stable dose of a statin used for at least for 1 month; (iii) no indication to decrease statin dose (symptoms are tolerable and CK level < 10x above ULR); (iv) expected to continue the same statin in the same dose during study period (as lipid

targets are achieved or muscle symptoms are likely to increase with increasing statin dose); (v) patient has signed informed consent for participation in the study.

Patients were excluded from the study if they met any of the following criteria: Exclusion criteria: CK level > 10 x ULR; muscle symptoms were present before statin therapy; regular intramuscular injections; serious suspicion of other cause of muscle symptoms; myocardial infarction or extensive surgery, or major trauma during the last one month; any surgery during last 2 weeks (except of PCI); elective surgical procedure in next 2 months (except for PCI); concomitant use of fibrates, nicotinic acid, red yeast extract, grapefruit juice, macrolide antibiotics, oral antifungal drugs, HIV protease inhibitors, cyclosporine, oral glucocorticiods (if change in dosage expected in the following 2 months), fluoxetine (if change in dosage expected in the following 2 months); liver enzyme elevation (AlAT or AsAT > 3 x ULR and/or conjugated or unconjugated bilirubin > 2 x ULR, with exception for Gilbert's syndrome), glomerular filtration rate < 30 ml/min as calculated by Cockroft-Gault formula; hyperkalemia ≥ 5 mmol/l; excessive consumption of alcohol (> 5 units daily); established neuromuscular pathology, rheumatic polymyalgia, mitochondrial myopathies; established clinically significant hypothyroidism with planned change in thyroxine dosage; known or suspected poor compliance; any disease associated with poor life expectancy; regular excessive physical exertions; drug abuse; inability to perform exercise test; pregnancy or a possibility of conception during the following next 2 months; known intolerance of polyprenols or CoQ10; and allergies to conifer trees.

All patients received supplementation with conifer-tree needle polyprenols (4 mg daily) and CoQ10 (100 mg daily) for 8 weeks in the form of two food supplements registered in Latvia: 2 capsules of "Poliprenols" ® (containing 1 mg of needle-tree polyprenols) and one capsule of "Kardiopren" ® (containing coenzyme Q10 100 mg and conifer-tree polyprenols 2mg). [12, 13].

2.2. Data collection

After the baseline visit, two follow-up visits were planned: at 4 weeks (± 7 days) and at 8 weeks (± 7 days). At the baseline as well as at 4 and 8 weeks patients were asked to evaluate subjective muscle symptoms (muscle pain, weakness, cramps) by self-assessment score (0-10), and to define which muscle groups are involved, and to report level of everyday physical activity defined as follows: low (<3 metabolic equivalents, METs), moderate (3-6 METs) and intensive (> 6 METs) activities measured in hours/per week.

The following investigations were performed at the baseline, at 4 weeks and at 8 weeks to evaluate safety and efficacy of the supplements: rest ECG; full blood count, plasma biochemical parameters (CK, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, alanine amino transferase (AlAT), aspartate amino transferase (AsAT), conjugated bilirubin, uncojugated bilirubin, glucose, creatinine, glomerular filtration rate (GFR) calculated according to Cockcroft-Gault formula, potassium, gamma-glutamyl transpeptidase (GGT), alcaline phosphatase (AP), high sensitivity C-reactive protein (hs-CRP); electroneuromyography (will be reported separately). The following investigations were performed at baseline and at 8 weeks: dynamometry

with Baseline® hydraulic hand dynamometer (3 measurements of grip strength in each arm, results registered in kg, the information about which arm is dominant was also recorded); exercise electrocardiography test (veloergometry) assessing load in wats (W), baseline and maximal heart rate in beats per minute (bpm), total ST depression sum in millimeters (mm), time until 1 mm ST depression in seconds (sec), heart rate/ST index; thyroid stimulating hormone (TSH), free thyroxin (FT4), free triiodothyronine (FT3) and 25-OH-vitamine D.

2.3. Statistical analysis

Statistical analysis was performed with IBM© SPSS© (version 22.0). Quantitative variables were described as mean value and standard deviation with exception of variables with non-normal distribution in which case median and interquartile range is reported. Categorical variables were described by amount and percentage. When two independent groups were compared, t-test for independent samples, Mann-Whitney U test, chi-square test and Fisher's exact tests were used as appropriate.

Repeated measures ANOVA was used to test significance of changes in quantitative variables during study period. In cases when assumption of sphericity was violated as estimated by Mauchly's test of sphericity, Greenhouse-Geisser correction was used. Sidak adjustment was used for pairwise comparisons. Quantitative variables with non-normal distributions were tested with non-parametric Friedman's test for repeated measures. Changes of binary variables in repeated measures were tested with Cochran's Q test. P values less than 0.05 were considered as statistically significant.

3. Results

3.1. Baseline characteristics

Of 14 patients (7 men and 7 women) enrolled in the study, 11 completed it *per protocol* (Figure 1). Two patients withdrew informed consent during the study. One patient was not willing to undergo repeated electromyography scheduled at 8 weeks. Another patient was unable to attend 8 weeks follow-up due to work assignments abroad. The study agents were discontinued by an investigator in the third patient due to liver safety concerns, which is described separately (see below *Safety*). The baseline characteristics of *per protocol* group and three excluded patients are summarized and compared in Table 1. Alcaline phosphotase levels were significantly lower in excluded group, and no other parameters were significantly different. Statin doses and muscle symptoms are given in Table 2. The localization of the muscle symptoms in per protocol group was the following: hips/thighs (n=7, 63.4%), calves (n=7, 63.4%), upper arms (n=4, 36.4%), lower arms (n=2, 18.2%), lower back (n=3, 27.3%), upper back and other locations were less prevalent (n<3). None of patients received other lipid-lowering drugs. The mean duration of statin treatment at the current dose before inclusion in the study was 9.9 ± 11.6 months (range: 1 to 36 months) in the total sample. The corresponding treatment duration was 10.8 ± 12.9 months (range: 1 to 36 months) and 6.6 ± 5.2 (range: 2 to 12 months) in *per protocol* and excluded groups, respectively (p=0.602). History of previous statin dose reduction due to muscle symptoms or CK elevations was reported by 7 patients (63.6%) and 3 patients (100%) in per protocol and excluded groups, respectively (p=0.505). Five (45.5%) and one (33.3%) patients reported previous intolerance of other than currently used statin in respective groups. Five patients (45.5%) had a history of intolerance of at least one another statin. Majority of patients had established atherosclerotic cardiovascular disease (Table 1). At the entry only 4 out

of 14 patients (28.6%) had reached their therapeutic target of LDL-C below 1.8 mmol/l. The safety and efficacy findings are reported for *per protocol* group. The results of electromyography will be reported separately.

3.2. Safety

None of the patients in *per protocol* group (n=11) experienced major adverse events during the 8 weeks. One patient underwent uncomplicated elective PCI during the study between week 4 and 8. No statistically significant increase was observed in levels of studied biochemical, hematologic and ECG variables (Table 3). There was a statistically significant mild reduction of triglyceride levels (p=0.023). Higher CK levels at 8 weeks were observed, but were not statistically significantly different from those at baseline and at 4 weeks (p=0.765 and p=0.718, respectively; Sidak adjustment for multiple comparisons). Three patients had CK levels >ULR at the baseline. At 4 and 8 weeks 5 and 4 patients had such elevations of CK, respectively (p=0.223).

One patient (65 years old female) was excluded from the study due to asymptomatic increase of liver enzymes at 4 weeks follow-up visit. The summary of the relevant biochemical data are given in Table 4. Considering liver enzyme elevations more than 3 times above ULR the statin (20 mg atorvastatin used for 7 weeks before inclusion and continued at the same dose during the study) was also discontinued. After 1 week of follow-up rapid normalization of the biochemical parameters was observed (Table 4). Other possible hepatotoxic factors were excluded (negative foe viral hepatitis B and C, no structural changes in liver and biliary system on ultrasound, patient denied use of any other drugs or substances). These changes were not accompanied by any symptoms or increase in CK or bilirubins. Of note, the patient had chronic kidney disease with GFR 50 ml/min, mild subclinical hypothyroidism (TSH 4.2 mU/L with URL 4.0 mU/L), and mildly decreased 25-OH-vitamin D levels (21.81). The renal function, however, did not worsen.

3.3. Efficacy

3.3.1. Muscle symptoms

Gradual and significant self-reported improvement of muscle pain (n=10) and weakness (n=7) was observed during the follow-up over 8 weeks according to self-assessment symptom scores (p<0.001 and p=0.018, respectively; figure 2). Regarding muscle pain there was a statistically significant improvement at weeks 4 and 8 compared to baseline (p=0.010 and p=0.001, respectively), but not at week 8 compared to week 4 (p=0.070). Reduction of muscle cramp severity (n=5) was not statistically significant across the study (p=0.069), but differed at week 8 compared to baseline (adjusted p=0.012, figure 2).

Muscle pain completely disappeared in 2 patients (20%), and four patients (40%) observed the reduction of the muscle pain score by at least 50%. The score did not change in 1 patient, and decreased by less than 50% in 3 patients. Muscle weakness completely resolved in 3 patients (42%), did not change in 2 patients (29%) and decreased by less than 50% in 2 patients (29%). Cramps disappeared in two patients (40%) and decreased by at least 50% in other two patients (40%), while did not change in one patient (20%).

Overall, among 11 patients completing the study only 2 patients did not have any improvements of any of their symptoms. At the end of the study 4 (40%) out of 10 patients in whom there was an indication to use higher than previously maximal tolerated statin dose, assessed subjective symptoms as having improved enough to consider up-titration of statin dose. One (10%) of patients had such improvement at week 4.

3.3.2. Dynamometry, exercise test and physical activities.

All patients reported right arm as the dominant. The maximal and average results of the three measurements for each arm did not change during the study (Table 5). No changes in any parameters of exercise veloergometry test were observed. The self-reported mild physical activities increased during the study (33.27 ± 12.56, 35.82 ± 16.20 and 39.55 ± 18.93 hours per week at baseline, 4 and 8 weeks, respectively, p=0.008, Figure 3).

4. Discussion

To our knowledge this is the first pilot study evaluating safety and efficacy of polyprenols in combination with CoQ10 in patients with SIM symptoms. Although this combination appeared to be generally well tolerated and safe in the majority of patients, we observed significant, but asymptomatic and reversible elevations of liver enzymes in one case. The patient was female with GFR <60 ml/min and mild subclinical hypothyroidism, mild vitamin D deficiency and no compelling evidence of liver disease. It is impossible to conclude if any of these factors alone or in combination were predisposing the patient to this event. The role of the baseline statin treatment on liver enzyme elevations cannot be ruled out either. Nevertheless, for future studies we recommend to either avoid the combination of polyprenols and CoQ10 in patients with GFR <60 ml/min or monitor such patients closely if any of these factors are present. If polyprenols are used, for safety reasons we currently recommend to test liver enzymes and CK levels at 4 weeks routinely, and to consider these tests at 2 weeks in patients with GFR <60 ml/min and/or with elevated TSH. The role of vitamin D deficiency as a risk factor for hepatotoxicity, however, seems less likely, as the mean 25-OH-vitamine D level was low in most patients of per protocol group (24.17$\pm$6.17 ng/ml), although higher than in the patient with elevated liver enzymes (21.81 ng/ml). Of note, only two out of 11 patients in *per protocol* group had normal vitamin D levels >=30 ng/ml, an intriguing finding in the context of previous reports suggesting vitamin D deficiency as a risk factor of statin induced muscle symptoms [14,15].

Contrary to our expectations, we did not observe reduction of CK levels. Moreover, there appeared to be some increase of CK levels during 8 weeks, which was not significant, but clinical relevance cannot be ruled out. It should be noted that the distribution of CK in the study sample was negatively skewed and non-parametric

Friedman's test for repeated measures was therefore applied. Thus small sample size in combination with lower power of the non-parametric tests leaves high probability of type 2 statistical error. Irrespectively, we recommend to closely monitor CK levels in future studies of polyprenols alone or in combination with CoQ10, especially in patients with CK levels in the range of 5 to 10 times above the ULR. Having said that, we found no evidence of worsened muscle symptoms in patients with increase of CK levels, and there was no correlation of CK changes with regression of muscle symptoms. Clearly, if confirmed, the significance and mechanisms of CK changes with polyprenols should be further investigated.

The study has several limitations. Our attempt to develop very stringent criteria to select "true" SIM patients lead to a small sample size. These patients were selected at the Latvian Center of Cardiology, among thousands of patients during 18 months. The challenge was to find patients meeting inclusion criteria, and there were very few cases where patients could not be included because of the exclusion criteria. This reiterates previous observations that the true prevalence of statin induced myopathies is much lower than commonly perceived. The current study was planned before the publication of the EAS scientific statement [3] and we therefore did not calculate the proposed statin myalgia clinical index score [4]. In the future research of polyprenols this score should be used for selection and characterization of the patients at the study entry.

This was an open-label, non-controlled, single center study, and all the results should be therefore interpreted with caution. Thus, the placebo effect and potential observer bias cannot be ruled out. Nevertheless the clinical efficacy surpassed the expectations of the investigators and was appreciated by several patients. Seven of them expressed willingness to continue the study agents after the completion of the

study, as they are available as food supplements. Importantly, 4 patients were ready to increase the dose of statin at the end of the study.

The results should be put into context of the fact that all patients received only combination of polyprenols and CoQ10, which does not allow to distinguish the effects of either of the two agents. The design of the study was planned before the publication of metanalysis of randomized trials of effects of CoQ10 on SIM with CoQ10 monotherapy [9], and at that time the study authors felt that many patients would benefit from CoQ10. Hence, it was planned as the pilot study to test if the combination is safe and if there is a signal of clinical efficacy. Based on the current findings there is a rational to perform randomized double-blind placebo controlled prospective parallel group study where monotherapy of polyprenols and combination of polyprenols with CoQ10 are tested against each other and placebo to clarify the role of polyprenols in alleviation of the statin induced muscle symptoms.

5. Conclusions

Conifer-tree polyprenols in combination with CoQ10 may be generally safe in patients with SIM, but caution should be exercised in patients with glomerular filtration rate <60 ml/min and routine monitoring of the liver enzymes and CK is advocated in all patients. Significant improvement of SIM symptoms observed in this study provides the rational for larger, double-blind controlled study with polyprenols.

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Table 1. Baseline characteristics of the study patients.

	Per protocol group (n=11)	Excluded (n=3)
Female gender (n, %)	5 (45.5%)	2 (66,7%)
Age, years (mean, SD)	67.73 ± 8.59	55.00 ± 18.19
History of coronary heart disease	11 (100%)	3 (100%)
Myocardial infarction	6 (54.5%)	1 (33.3%)
PCI	8 (72.7%)	2 (66.7%)
CABG	1 (9.1%)	1 (33.3%)
Peripheral artery disease	2 (18.2%)	0
Blood biochemistry (mean, SD)		
Total cholesterol, mmol/l	4.45 ± 1.24	4.30 ± 0.78
Triglycerides, mmol/l	2.25 ± 1.39	1.56 ± 0.75
HDL-cholesterol, mmol/l	1.33 ± 0.27	1.09 ± 0.24
LDL-cholesterol, mmol/l	2.25 ± 0.95	2.76 ± 0.83
Glucose, mmol/l	5.43 ± 0.77	5.53 ± 1.06
Creatine kinase (CK), U/l	240.09±303.08	236.00 ± 204.21
CK >ULR (n, %)	2 (18.2%)	1 (33.3%)
AlAT, U/l	29.82 ± 11.69	32.22 ± 6.11
AsAT, U/l	34.27 ± 14.00	25.33 ±5.69
GGT, U/l	65.82 ± 74.83	22.33 ± 8.96
AP, U/l	89.91 ± 15.16	64.33 ± 3.21*
Conjugated bilirubin, μmol /l	3.85 ± 1.55	2.97 ± 0.91
Unconjugated bilirubin μmol /l	7.28 ± 2.37	5.20 ±1.06
Creatinine, μmol /l	73.18 ± 17.93	95.33 ±30.29
GFR ml/min	96.30 ± 25.61	97.67 ± 73.24
Potassium, mmol/l	4.60 ± 0.74	4.50 ± 0.26
TSH, mU/l	1.57 ± 1.25	2.37 ± 1.59
25-OH-Vitamin D, ng/l	24.17 ± 6.71	23.69 ± 5.06
hs-CRP mg/l (medium, IQR)	1.17 (0.97-2.47)	1.07 (-)
Other cardiovascular risk factors		
Smoking (n,%)	1 (9,09%)	0 (0%)
Hypertension (n, %)	8 (72.73%)	2 (66.66%)
Diabetes (n, %)	2 (18.18%)	0 (0%)
Body mass index, kg x m^{-2} (mean, SD)	27.96 ± 2.13	29.38 ± 5.53
Alcohol units per week (mean, SD)	2.18 ± 1.54	1.67 ± 1.16
Physical activities, h per week (mean, SD)	33.27 ±12.56	28.00 ± 12.12
Mild	7.27 ± 8.46	8.33 ± 5.13
Moderate	1.18 ± 3.06	0
Intensive		

PCI – percutaneous coronary intervention, CABG - coronary artery bypass graft surgery, ULR - upper limit of reference range, SD - standard deviation, IQR - interquartile range, LDL - low density lipoprotein, HDL - high density lipoprotein, AlAT - alanine amino transferase, AsAT - aspartate amino transferase, GFR - glomerular filtration rate, GGT - gamma-glutamyl transpeptidase, AP - alcaline phosphatase, hs-CRP - high sensitivity C-reactive protein, TSH - thyroid stimulating hormone

* p=0.015, all other p>0.05.

Table 2. Statin therapy and muscle symptoms at the inclusion.

* Symptom severity score based on subjective symptom assessment by a patient (range 0 to 10). The score is calculated only for the patients with presence of the

	Total (n=14)	Per protocol (n=11)	Excluded (n=3)
Statin therapy			
Atorvastatin 20 mg (n)	2 (14.29%)	1 (9.09%)	1 (33.33%)
Atorvastatin 30 mg (n)	1 (7.14%)	1 (9.09%)	-
Atorvastatin 40 mg (n)	1 (7.14%)	1 (9.09%)	-
Rosuvastatin 5 mg (n)	2 (14.29%)	1 (9.09%)	1 (33.33%)
Rosuvastatin 10 mg (n)	3 (21.43%)	3 (27.27%)	-
Rosuvastatin 20 mg (n)	4 (28.57%)	3 (27.27%)	1 (33.33%)
Rosuvastatin 40 mg (n)	1 (7.14%)	1 (9.09%)	-
Muscle symptoms and signs			
Pain (n, %)	13 (92.86%)	10 (90.90%)	3 (100%)
Pain at rest (n, %)	11 (78.57%)	9 (81.82%)	2 (66.67%))
Pain severity score (mean, SD)*	5.69 ± 1.84	6.00 ± 1.70	4.67 ± 2.31
Weakness (n, %)	8 (57.14%)	7 (63.64%)	1 (33.33%)
Weakness severity score (mean, SD)	6.00 ± 1.51	6.14 ± 1.57	5.00
Cramps (n, %)	6 (42.86%)	5 (45.46%)	1 (33.33%)
Cramps severity score	5.33 ± 2.58	6.00 ± 2.34	2.00
Elevated CK levels >ULR	577.00±342.46	614.00±409.51	466.00±0

symptom.

CK - creatine kinase, ULR - upper limit of reference range, SD - standard deviation

Table 3. Safety parameters.

Mean, SD	Baseline	4 weeks	8 weeks	p value*
Blood biochemistry				
Total cholesterol, mmol/	4.45 (1.24)	4.05 (0.62)	4.23 (0.57)	0.259
Triglycerides, mmol/l	2.25 (1.39)	1.72 (1.16)	1.87 (0.95)	0.023
HDL-cholesterol, mmol/l	1.33 (0.27)	1.32 (0.27)	1.37 (0.23)	0.844
LDL-cholesterol, mmol/l	2.25 (0.95)	1.99 (0.54)	2.02 (0.58)	0.305
Glucose, mmol/l	5.34 (0.77)	5.35 (0.77)	5.46 (0.67)	0.810
Creatine kinase, U/l **	107 (85-275)	176 (97-214)	178 (92-216)	0.231***
AlAT, U/l	29.82 (11.69)	29.36 (8.87)	31.27 (12.91)	0.796
AsAT, U/l	34.27 (13.99)	32.64 (11.29)	35.36 (19.03)	0.648
GGT, U/l	65.81 (74.83)	58.18 (61.60)	46.18 (38.36)	0.286
AP, U/l	89.91 (15.16)	86.64 (19.72)	82.00 (13.52)	0.338
Conjugated bilirubin, µmol/l	3.85 (1.55)	4.03 (1.45)	3.54 (1.31)	0.538
Unconjugated bilirubin, µmol/l	7.28 (2.37)	7.48 (2.22)	6.98 (2.28)	0.624
Creatinine, µmol/l	73.18 (17.93)	71.64 (19.97)	73.00 (22.62)	0.292
GFR, ml/min	96.30 (25.61)	100.70 (30.35)	98.30 (28.90)	0.275
Potassium, ml/min	4.59 (0.74)	4.84 (0.72)	4.49 (0.28)	0.333
TSH, mU/l (n=10)	1.57 (1.25)	-	2.07 (1.44)	0.059
25-OH-Vitamin D, ng/l (n=10)	24.17 (6.71)	-	23.48 (8.27)	0.571
hs-CRP, mg/l **	1.17 (0.97-2.47)	1.53 (0.99-3.61)	1.86 (0.83-4.70)	0.477****
Haematology				
Red blood cells, 10x12/L	4.86 (0.20)	4.79 (0.36)	4.79 (0.36)	0.599
White blood cells, 10x9/L	11.03 (12.10)	7.65 (2.47)	7.50 (1.92)	0.390
Platelets, 10x9/L	248.91 (37.70)	261.55 (34.45)	244.55 (37.32)	0.110
Haemoglobin, g/L	144.27 (8.84)	140.55 (11.64)	140.91 (13.19)	0.235
Electrocardiography				
Sinus rhythm (n, %)	9 (81.8%)	9 (81.8%)	9 (81.8%)	1.000
Heart rate (bpm)	71.91 (14.87)	63.18 (9.05)	67.64 (8.42)	0.097
PR (ms) (n=9)	169.89 (30.23)	175.78 (36.49)	174.67 (30.97)	0.516
QRS (ms)	106.27 (24.46)	107.27 (24.73)	106.55 (23.24)	0.779
QT (ms)	407.27 (41.69)	427.45 (33.36)	412.00 (29.85)	0.125
QTc (ms)	382.82 (43.52)	394.27 (34.04)	371.64 (25.874)	0.217

* Repeated measures ANOVA; ** median and interquartile range; *** Friedman's test; **** median and interquartile range, comparisons performed with logarithmically transformed values; ***** in patients with sinus rhythm (n=9).

SD - standard deviation, LDL - low density lipoprotein, HDL - high density lipoprotein, AlAT - alanine amino transferase, AsAT - aspartate amino transferase, GFR - glomerular filtration rate, GGT - gamma-glutamyl transpeptidase, AP - alcaline phosphatase, hs-CRP - high sensitivity C-reactive protein, TSH - thyroid stimulating hormone, PR – PR interval, QRS – QRS complex, QT- QT interval, QTc - corrected QT interval

Table 4. Summary of the patient case with liver enzyme elevations.

	Baseline	4 weeks	+1 day FU	+7 days FU	Reference limits
AlAT	31.00	473	313	62	< 41 U/l
AsAT	27.00	189	82	34	< 37 U/l
GGT	28.00	282	250	154	< 61 U/l
AP	62.00	151	134	90	< 117 U/l
Total bilirubin	6.00	5.60	-	6.20	< 19 μmol/l
Conjugated bilirubin	2.00	1.70	-	-	< 3,4 μmol/l
Unconjugated bilirubin	4.00	3.90	-	-	- μmol/l
CK	166	191	-	-	190 U/l
Creatinine	130.00	113	-	-	30-106 μmol/l
GFR	50	58	-	-	>90 ml/min
Potassium	4.70	4.90	-	-	3.50-5.30 mmol/l)
25-OH-vitamine D	21.81	-	-	-	30-100 ng/ml
hs-CRP	1.60	2.49	-	-	<1.0 mg/l

FU – follow-up, AlAT - alanine amino transferase, AsAT - aspartate amino transferase, GGT - gamma-glutamyl transpeptidase, AP - alcaline phosphatase, CK – creatine kinase, GFR - glomerular filtration rate, hs-CRP - high sensitivity C-reactive protein

Table 5. Physical tests (n=11).

	Baseline	4 weeks	8 weeks	p value*
Dynamometry				
Right arm, maximum (kg)	39.73 (20.80)	38.36 (20.09)	40.36 (22.77)	0.425
Right arm, average (kg)	35.94 (20.21)	35.88 (18.94)	36.09 (20.03)	0.985
Left arm, maximum (kg)	35.18 (20.83)	36.45 (20.97)	39.36 (18.60)	0.047
Left arm, average (kg)	33.09 (20.31)	34.73 (20.17)	36.91 (18.09)	0.102
Exercise test	106.82 (37.23)	-	100.00 (29.58)	0.192
Load (watts)	107.36 (18.05)	-	108.73 (15.14)	0.728
Peak pulse (bpm)	172.18 (17.53)	-	160.00 (23.18)	0.087
Peak SBP (mmHg)	89.82 (6.13)	-	94.73 (17.60)	0.443
Peak DBP (mmHg)	2.23 (1.77)	-	1.96 (1.10)	0.433
ST depressions (mm)	1.00 (1.02)	-	1.24 (1.03)	0.609
Heart rate / ST index (bpm/mm)				

SBP - systolic blood pressure, DBP - diastolic blood pressure
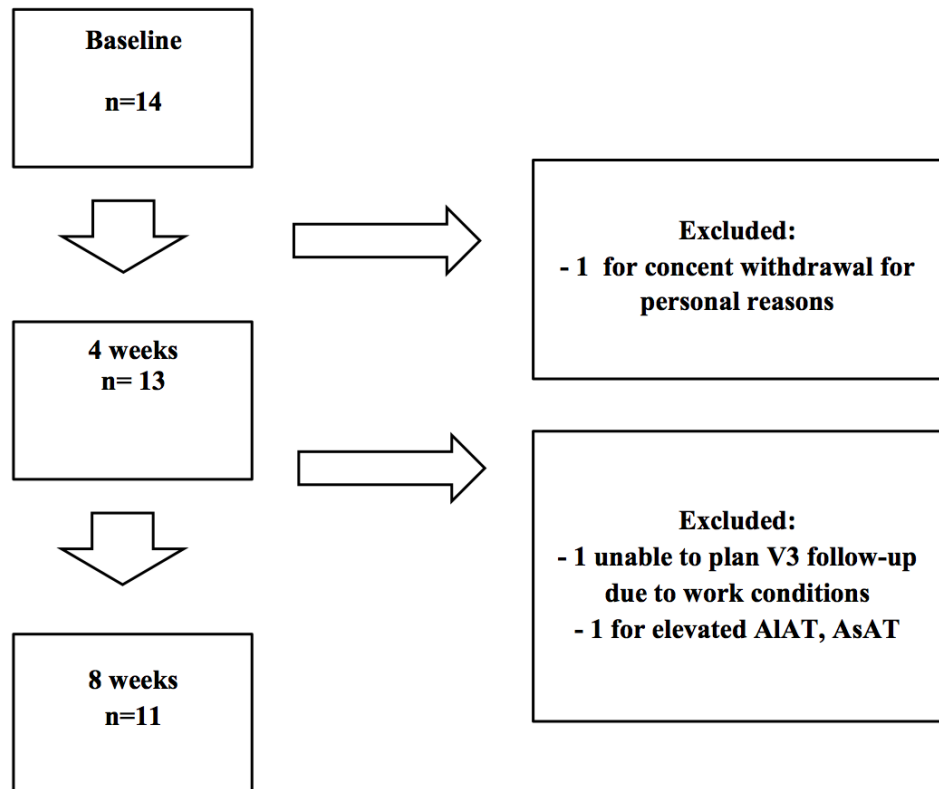
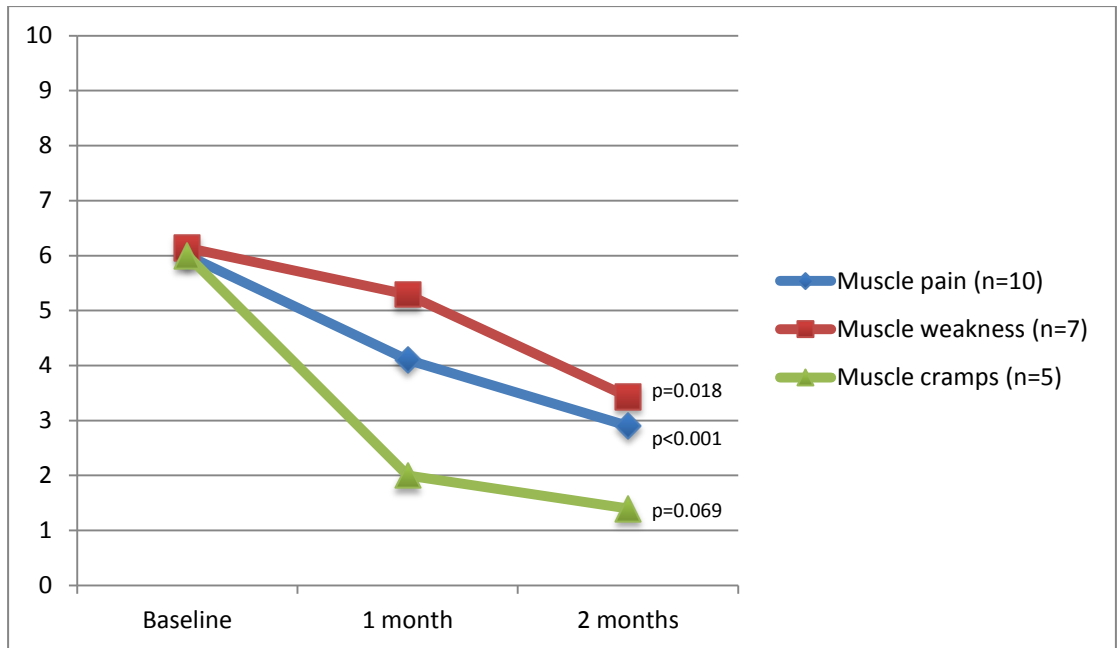**Figure**

Figure 1. Study flow diagram.

Figure 2. Self-reported muscle symptom scores during the study period.

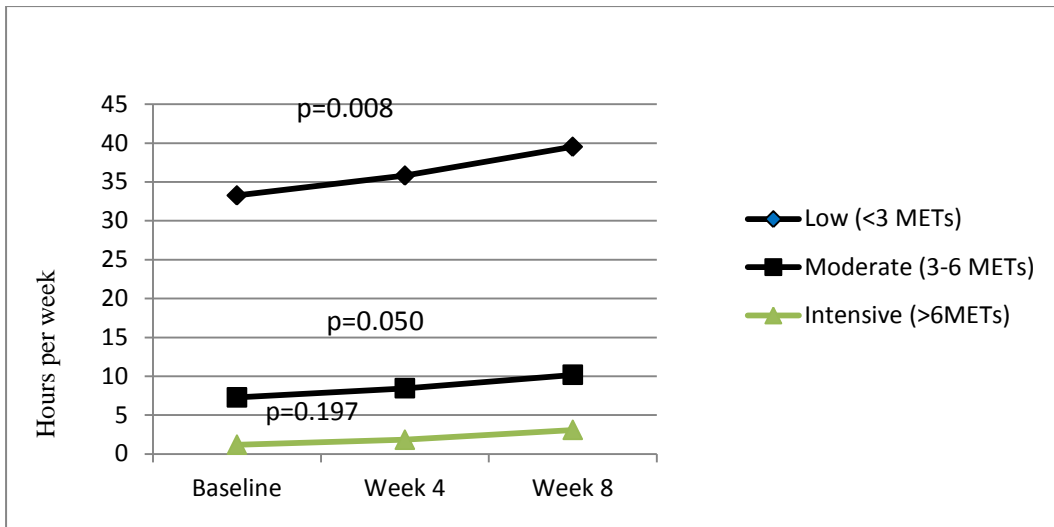P values represent statistical significance across all repeated measurements.

Figure 3. Self-reported physical activities in hours per week (n=11).