Original Article

Statin-associated muscle symptoms in coronary patients – design of a randomized study

John Munkhaugen[a,b*], Nils Tore Vethe[c], Morten Wang Fagerland[d], Toril Dammen[b], Joep Perk[e], Erik Gjertsen[a], Jan Erik Otterstad[f], Lars Gullestad[g], Stein Bergan[c,h] & Einar Husebye[a]

[a]Department of Medicine, Drammen Hospital, Vestre Viken Trust, Drammen, Norway; [b]Department of Behavioural Science in Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway; [c]Department of Pharmacology, Oslo University Hospital, Oslo, Norway; [d]Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo, Norway; [e]Linneus University, Kalmar, Sweeden; [f]Department for Cardiology, Vestfold Hospital Trust, Tønsberg, Norway; [g]Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [h]School of Pharmacy, University of Oslo, Oslo, Norway

***Corresponding author:** John Munkhaugen, MD, PhD, Department of Medicine, Drammen Hospital, Vestre Viken Trust, Dronninggata 41, 3004 Drammen, Norway.

E-mail: johmun@vestreviken.no

Short title: Design of statin muscle side-effects study

Manuscript word count (without references): 3069

Statin-associated muscle symptoms in coronary patients – design of a randomized study

Abstract

Objectives

Estimate the effect of atorvastatin on muscular symptom intensity in coronary patients with subjective statin-associated muscle symptoms (SAMS) and to determine the association with blood levels of atorvastatin and its metabolites, to obtain an objective marker for true SAMS.

Design

A randomized, double-blinded, cross-over study will include 80 coronary patients with subjectively reported SAMS during ongoing atorvastatin therapy or previous muscle symptoms that led to discontinuation of atorvastatin. Patients will be randomized to 7-weeks treatment with atorvastatin 40 mg/day in the first period and matched placebo in the second 7-weeks period, or placebo in the first period and atorvastatin in the second period. Each period is preceded by 1-week wash-out. A control group (n=40) without muscle symptoms will have 7 weeks open treatment with atorvastatin 40 mg/day. Blood samples will be collected at baseline and at the end of each treatment period, and muscular symptoms will be rated by the patients weekly using a Visual Analogue Scale (VAS). The primary outcome is the difference in aggregated mean VAS scores between the last three weeks of atorvastatin treatment and of placebo treatment. The main purpose is to develop an objective marker for true SAMS, by comparing SAMS associated with blinded atorvastatin treatment with blood concentrations of atorvastatin and its metabolites. Diagnostic and discrimination performance will be determined.

Conclusions

The study provides new knowledge on SAMS in coronary patients and may contribute to more personalized statin treatment and monitoring, fewer side-effects and consequently improved adherence and lipid management in future practice.

Abstract word count: 250

Keywords: Atorvastatin, statin-associated muscle symptoms (SAMS), coronary heart disease, LC/MS-MS, pharmacogenetics, psychosocial factors, randomized controlled trial

Introduction

Statins are recommended (1, 2) and cost-effective (3) drug treatment to reduce low-density lipoprotein cholesterol (LDL-C) with improvement of cardiac outcomes in coronary heart disease (CHD) patients. (1, 2) Statin treatment is, however, far from optimal in clinical practice. International (4) and own data from the NORwegian-CORonary Prevention Study (5) have revealed that 7-12% of the CHD patients did not use statin therapy at all, whereas 57-80% of those on statin therapy still have LDL-C levels above the recommended target level of 1.8 mmol/L. Statin-associated muscle symptoms (SAMS) is one of the principal reasons for statin non-adherence and/or discontinuation leading to adverse cardiac outcomes, and may adversely influence the patient's quality of life, muscle strength and ability to perform daily activities. (6, 7)

Serious statin side-effects are rare (6, 7) and were only reported in a minority (i.e. 1-5%) of CHD patients participating in randomized placebo-controlled statin trials.(8) SAMS, however, comprises a heterogeneous group of muscle symptoms including pain, aching, stiffness, tenderness or cramps, usually with normal or minimally elevated creatine kinase levels, amounts to 20-30% in observational studies (9). Strict entry criteria in the randomized trials, excluding patients with polypharmacy, comorbidities, elderly, females and low body weight, all factors that predispose to musculoskeletal symptoms, may in part explain variations in frequency of SAMS among these populations. (6, 7) Observational studies suffer from the absence of blinding. Patients on statins may expect side-effects, and therefore report a higher percentage of SAMS than untreated patients, the so-called 'nocebo' effect. In a population-based randomized, double-blinded cross-over study of patients complaining of SAMS, only 36% experienced that their muscle symptoms persisted during treatment with simvastatin 20 mg and disappeared during placebo treatment.(10) Accordingly, SAMS was confirmed to be

related to the statin treatment in only one-third of those reporting side-effects. The prevalence of confirmed SAMS in a CHD population, treated with potent statins according to the guidelines, (1, 2) remains unknown. (6)

Patients with psychosocial distress may be at increased risk of misattributing their symptoms to statins or being hypervigilant to true adverse effects of statins such as muscle pain.(11) In a randomized atorvastatin trial in patients without cardiovascular disease and depression, depression scores within normal range did not predict changes in muscle pain severity between the atorvastatin and placebo group after 6 months follow-up. (12) Anxiety symptoms have been associated with non-adherence to statin therapy and with increased pain perception, in general.(13) Type D personality is associated with pain perception, pain inference, and musculoskeletal pain.(14) The relationship between these psychosocial factors and SAMS remains to be investigated.

It remains unclear how statins may produce muscle symptoms and reliable biomarkers for the prediction or diagnosis of SAMS are lacking.(6,7) Individual variations in statin pharmacokinetics, mitochondrial dysfunction or coenzyme Q10 deficiency are suggested mechanisms for SAMS. (15) A few studies indicate that pharmacokinetic alterations in statin metabolites may contribute to SAMS. (16-18) The lactone metabolites of statins seem to be more potent in inducing myotoxic effects compared to the corresponding acid metabolites. Plasma concentrations of atorvastatin lactones have been associated with clinical muscle symptoms.(17, 18) Accordingly, the lactones inhibit the mitochondrial complex III enzyme activity, thereby reducing the respiratory capacity in muscle cells.(19) We have recently developed and validated a fast, sensitive, and reliable liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for precise quantification of atorvastatin and its major

lactone and acid metabolites in blood.(20) The acyl glucuronide of atorvastatin is also included because acyl glucuronide metabolites of drugs are associated with toxicity.(21) Atorvastatin or metabolite levels have previously not been investigated as diagnostic markers of SAMS, under randomized, blinded and placebo-controlled conditions.

Study objectives and hypothesis

The overall objective is to provide new clinical and pathophysiologic knowledge of SAMS in CHD patients that enables reliable detection and confirmation of pharmacologically true SAMS. The primary, secondary and exploratory objectives are listed in *Table 1*. Based on previous evidence, (10) the primary hypothesis is that true SAMS will be identified in 30-40% of the patients with subjectively reported SAMS during treatment with atorvastatin compared to placebo. The secondary hypothesis is that patients with placebo-controlled SAMS will have higher levels of atorvastatin and/or its metabolites than the patients without placebo-controlled SAMS, and that true SAMS can be identified with high sensitivity and specificity. We also hypothesize that atorvastatin and metabolite levels will not differ between the control group without muscle symptoms and the patients failing the placebo-test for connecting SAMS to atorvastatin.

Material and methods

Study design

This is a randomized, double-blinded, multi-center, cross-over study that will include 80 CHD patients with either subjective SAMS during ongoing atorvastatin therapy or previous muscle symptoms that led to discontinuation of atorvastatin. The patients will be randomized to atorvastatin in the first period and placebo in the second period or placebo in the first period and atorvastatin in the second period (AB/BA cross-over design). The study flow chart is shown

in *Figure 1*. A control group of 40 coronary patients on atorvastatin without previous or ongoing muscle symptoms will have 7 weeks open treatment with an atorvastatin dose similar to that used in the cross-over arms.

Study population and recruitment

The study will be conducted at two Norwegian hospitals (Drammen and Vestfold). Consecutive patients undergoing a first or recurrent CHD event will be identified from hospital discharge lists and screened through a standardized telephone interview. All patients reporting subjective SAMS during ongoing atorvastatin therapy, or with previous muscle symptoms on atorvastatin that has led to discontinuation will be invited to the outpatient clinics for eligibility evaluation. A random selected control group will be recruited similarly. Further details on study entry criteria are summarized in *Table 2*.

Randomization and interventions with study drug

If all eligibility criteria are met and written informed consent is provided, patients will be randomized to double-blinded prescription of atorvastatin or a matched placebo tablet in a 1:1 ratio. Block randomization with block size 4 and 6 in random order, stratified according to centre and previous statin discontinuation, will be used. The recommended and most frequently used dose of atorvastatin in CHD patients, tablets of 40 mg once daily, is chosen. After randomization, all patients will undergo a 1-week pharmacokinetic wash-out before start-up with study medication (*Figure 1*). All participants in the randomized study will then be treated for 7 weeks or until muscle symptoms are intolerable. After a second 1-week wash-out patients will be switched from atorvastatin to placebo or vice versa for a subsequent 7-weeks period. In total, study participation comprises 3 clinical visits with blood sampling per patient. Previous data from two observational studies using atorvastatin, indicate that 7-weeks of treatment or

non-treatment are sufficient for muscle symptoms to appear and disappear in 100% and 80% of these patients, respectively. (22, 23)

All study patients will receive an information letter stating that they participate in a clinical trial, containing information about the sponsor, contact information to study staff and information about contraindicated foods and drugs that interact strongly with atorvastatin. Patients will be instructed to wear this letter in case of medical contact.

Blinding

The participant and study staff will all be blind to the participant's sequence allocation. Placebo tablets will be manufactured specially to match the atorvastatin by the manufacturer. Capsules and packaging will be identical in appearance for both active treatment and placebo. Unblinding will be available within 24 hours in case of Suspected Unexpected Serious Adverse Reactions or if clinical management depends importantly on knowledge of whether the patient is currently receiving atorvastatin or placebo.

Data collection and monitoring

A detailed overview of the study data collected is shown in *Table 2*. Data from hospital medical records will be collected at baseline, whereas self-report questionnaire data and blood samples will be collected at baseline and at the end of each treatment period. Muscle symptoms and the likelihood for these symptoms to result in statin discontinuation will be registered weekly in a diary. Blood samples for statin concentration measurements will be collected immediately before the morning dose and 2 hours after observed tablet intake in the end of each 7-weeks treatment period. This sampling scheme will allow both the trough and peak exposure of the

drug to be investigated as diagnostic markers of SAMS. Clinical and genetic covariates that may explain diversity in the pharmacokinetics of atorvastatin and its metabolites will be assessed.(6, 7) Patients who experience intolerable muscle symptoms will have blood samples collected within 48 hours to prevent discontinuation before sampling.

Pharmacokinetic pilot data

We have pilot data indicating that the atorvastatin lactone/acid ratio is three-fold higher in white blood cells (i.e. lymphocytes) compared with plasma. Atorvastatin and metabolites levels in white blood cells is therefore also a relevant candidate marker for SAMS. Furthermore, pilot data indicate higher dose-normalized levels of the potential myotoxic 4-OH-atorvastatin lactone in patients reporting muscle symptoms (n = 3) compared with those not reporting muscle symptoms (n = 6). At 2 hours after dosing the patients with muscle symptoms had on average 2.3-fold higher lactone concentration (0.41 ± 0.28 vs. 0.18 ± 0.08 nmol/L).

Adherence to study treatment by indirect methods

Study participants will report adherence to study treatment weekly in the diary. In addition, remaining pills in returned packages will be counted by the study nurse after each treatment period.

Safety monitoring and risk evaluation

Potential risks include adverse cardiovascular events during the 8-week period without atorvastatin and serious statin side-effects during treatment with atorvastatin. In a large randomized statin trial, 6 weeks statin discontinuation in CHD patients did not lead to increased risk of subsequent cardiovascular events.(25) Swedish real world data in CHD patients have documented that the risk of subsequent cardiovascular events are highest during the first 12

months.(26) A short-term discontinuation of statin therapy of maximum 8 weeks required for study implementation is therefore regarded safe in patients fulfilling the entry criteria (*Figure 1*). All Serious Adverse Events will be continuously monitored by the study cardiologists. Suspected Unexpected Serious Adverse Reactions will be limited to symptoms and signs not listed in the Summary of Product Characteristics.

Outcome assessment

The primary, secondary and exploratory end-points are listed in *Table 1*. VAS scores over the last 3 weeks in each treatment period have been chosen as primary end-point for three reasons: i) to ensure steady state concentrations of atorvastatin; ii) to maximize the likelihood for the symptoms reported to being truly related to the current (and not previous) treatment period; iii) the duration of the treatment period being sufficiently long to produce SAMS (>3 weeks). VAS has also been chosen as primary outcome in two previous SAMS studies. (22, 23) A 25% intra-individual change in the VAS symptom score has been regarded clinically relevant in a previous validation study of the scale. (27) Accordingly, confirmed SAMS will be defined as a 25% higher individual VAS score during the treatment period on atorvastatin vs. placebo in our study.

Statistical considerations

Power calculations are based on the ability to detect a 1 cm difference in the VAS symptom score between the treatment periods on atorvastatin and placebo since the smallest change in VAS symptom score corresponding to ‘a little more’ or ‘a little less’ symptoms was 1.3 cm, with a lower limit of the confidence interval at 1 cm in a previous study.(27) Gallagher et al. (27) report a standard deviation of 1.7 for a difference of 1.0 between two VAS symptom scores. Due to the differences in populations and specific VAS scale between that study and the

present one, we use standard deviation =2.5 to account for a much larger variation in this study. With n=68, we will have 90% power to detect a difference of 1.0, using a one-sample T test. With n=68, we will also have 80% power to detect a difference of 40% SAMS under statins vs. 15% SAMS under placebo, using the McNemar test for paired probabilities. To account for missing data due to drop-outs and protocol deviations, 80 patients are included.

The primary outcome and all other continuous outcomes will be estimated with linear regression models with the stratification factors in the randomization as covariates. Dichotomous outcomes will be analysed with conditional logistic regression models. Methods for analysis of Receiver Operating Characteristic curves and measures of diagnostic accuracy will be used to identify cut-off values of metabolite concentrations that can discriminate between confirmed SAMS and other muscle symptoms. The correlations between muscular symptom intensity differences between treatment periods with statin and placebo and levels of atorvastatin and metabolites will be estimated with Spearman correlation coefficients and linear regression analyses. By study design (i.e. randomized, double-blinded) and due to evidence from previous SAMS studies, (22, 23) the likelihood of cross-over effects of period effects are regarded to be low. A detailed Statistical Analysis Plan will be written prior to database lock.

Study organization

Vestre Viken Trust is the sponsor for this investigator-initiated interdisciplinary trial. The steering committee composed of the primary investigator (JM), the steering committee members (EH, NTV, TD, SB, EG, LG, JEO, JP) and the study statistician (MWF) approved the study design and protocol, and will approve the statistical analysis plan prior to data base lock. Data collection and coordination will be under the responsibility of the participating centers together with the Clinical Trial Unit at Oslo University Hospital.

User involvement

The user-group comprising user-group representatives, general practitioners and cardiac nurses have provided feedback in the study design, the self-reported study questions and patient information lettersThe group will also play an important role in disseminating the study results.

Ethical and other regulatory approvals

The study will be conducted in accordance with the Declaration of Helsinki and are consistent with /Good Clinical Practice and applicable regulatory requirements and personal data laws. The protocol has been approved by the Regional Ethics Committee (2018/2302) and the National Medicines Agency (18/17102-16). The protocol has been registered at the European Clinical Trials Database (EudraCT number 2018-004261-14) and at clinicaltrials.gov (NCT03874156).

Study status and timeline

Based on evidence from the NOR-COR study, (5) we expect to identify at least 200 patients with present subjective SAMS on atorvastatin or with discontinued atorvastatin due to subjective SAMS, during the telephone screening. Based on the study entry criteria and significant non-participation rate, a conservative estimate is that 40% of these patients (n=80) along with the control group of n=40 may be enrolled over a 9 months period. Patient enrolment commenced in March 2019. With mean follow-up time at the end of inclusion of 3 months, the total study duration will be no more than 12 months. The results of primary and secondary endpoints are expected during spring 2020.

Post-trial care

The trial ends the day after completion of the last treatment day and the study blinding will then be uncovered. Recommendations for further lipid management will be given to the patients and their primary care physicians as soon as the study results are available. Patients with confirmed SAMS will be recommended rosuvastatin and subsequently proprotein convertase subtilisin kexin 9 [PCSK 9] inhibitors, if indicated.(28) Three to six months after study completion, the patients experiences with study participation and whether muscle symptoms still are present will be evaluated.

Strengths

New knowledge of SAMS and the identification of diagnostic biomarkers are raised as major needs in guidelines (1, 2) and Consensus documents. (6, 7) The present study addresses the major criticisms in previous studies of SAMS. The study is double-blinded and placebo-controlled and will thus confirm whether the patients' muscle symptoms are truly related to the statin therapy or not. Additionally, the within-patient comparisons of muscle symptoms experienced during statin treatment versus placebo and the measurement of statin and metabolite levels will enable us to determine the relationship between these blood levels and muscle symptoms in patients with and without confirmed SAMS. In addition, the study provides new knowledge about the clinical and psychosocial characteristics of patients with and without confirmed SAMS.

The LC-MS/MS method demonstrated to be accurate and precise over wide concentration ranges, and the lactone instability was controlled during the pre-analytical and analytical phases.(20) Our pilot data indicate higher atorvastatin metabolites levels in patients with subjective SAMS compared to those without SAMS. Thus, the present study may unravel the

origin of true SAMS and potentially paves the way for diagnostic testing of this condition. Moreover, the statin assay may identify patients in need of altered statin therapy or dose adjustments due to inadequate blood concentrations or intolerable side-effects associated with too high blood levels. Pharmacological data facilitate the communication to patients with subjective SAMS (i.e. the role that statin drugs play for their muscle symptoms), and thus prevent statin discontinuation, facilitate change of drug when indicated, and improve adherence. By adding a control group without muscle symptoms, we can also reveal whether atorvastatin and metabolites concentrations in study participants with subjective and non-confirmed SAMS (incorrectly assumed SAMS) are in line with blood concentrations in patients without muscle symptoms. Costs of new, expensive drugs to target subclinical inflammation (e.g. canacunimab) (29) and to lower lipids (e.g. PCSK 9 inhibitors)(28) are substantially higher than currently used statins. Therefore, optimizing treatment and adherence with cost-effective (3) statins is of outmost importance for the healthcare system. The study results are likely to translate to statin therapy in primary prevention. The potential impact on public health care is thus substantial.

Limitations

Patients who have previously experienced intolerable muscle symptoms during statin use may be unwilling to participate. Moreover, the study results are not representative for other statin classes. Atorvastatin is, however, currently used by the majority of CHD patients in Norway and Europe. (4, 5) Due to the relatively small sample size, the study results need to be confirmed in a large-scale statin trial if atorvastatin metabolites prove to be a sufficiently accurate diagnostic marker of SAMS. With 40 participants only in each treatment arm, the power is confined to a limited number of covariates, for comparing the treatment groups with regard to confirmed SAMS. Selection-bias is always a challenge in a randomized study setting and younger patients and those not living within a short distance from the hospital may refuse

participation. Finally, blood levels of atorvastatin and metabolites in patients with SAMS excluded from the study remains unknown.

Conclusion

The study will provide new clinical knowledge on SAMS in coronary patients and clarify the potential of statin measurements in the management of lipid control in CHD. This may contribute to a more personalized atorvastatin treatment and monitoring, fewer side-effects and consequently improved adherence and lipid management in future practice.

Acknowledgments

The study idea originates from the Department of Medicine, Drammen Hospital and the Department of Pharmacology, Oslo University Hospital. The clinical study will be carried out at the hospitals in Drammen and Vestfold. The concept is developed by the project in collaboration with communities at the University of Oslo.

Disclosures

The authors report no conflict of interest.

Funding details

This work was supported by the National Health Association, the Department of Medicine, Drammen Hospital, and the Department of Pharmacology, Oslo University Hospital.

Author contribution

JM, EH, NTV, SB, TD, JP, JEO, and LG contributed to the design of the work. JM prepared the figures and drafted the manuscript. NTV, EH, TD, MWF, and JEO contributed significantly to the preparation. All authors critically revised the manuscript and gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Reference

1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Circulation. 2014;129:S1-45.

2. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2016;23:Np1-np96.

3. Chaplin S, Scuffham PA, Alon M, et al. Secondary prevention after PCI: the cost-effectiveness of statin therapy in the Netherlands. Neth Heart J. 2004;12:331-6.

4. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol. 2016;23:636-48.

5. Munkhaugen J, Sverre E, Otterstad JE, et al. Medical and psychosocial factors and unfavourable low-density lipoprotein cholesterol control in coronary patients. Eur J Prev Cardiol. 2017;24:981-989

6. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J. 2015;36:1012-22.

7. Mancini GB, Baker S, Bergeron J, et al. Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Canadian Consensus Working Group Update (2016). The Canadian journal of cardiology. 2016;32:S35-65.

8. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006;114:2788-97.

9. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013;158:526-34.

10. Taylor BA, Lorson L, White CM, et al. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. Atherosclerosis. 2015;238:329-35.

11. Korhonen MJ, Pentti J, Hartikainen J, et al. Somatic symptoms of anxiety and nonadherence to statin therapy. International Journal of Cardiology. 2016;214:493-9.

12. Zaleski AL, Taylor BA, Pescatello LS, et al. Influence of Baseline Psychological Health on Muscle Pain During Atorvastatin Treatment. The Journal of Cardiovascular Nursing. 2017;32:544-50.

13. Kivrak Y, Kose-Ozlece H, Ustundag MF, et al. Pain perception: predictive value of sex, depression, anxiety, somatosensory amplification, obesity, and age. Neuropsychiatric disease and treatment. 2016;12:1913-8.

14. Talaei-Khoei M, Mohamadi A, Fischerauer SF, et al. Type D personality in patients with upper extremity musculoskeletal illness: Internal consistency, structural validity and relationship to pain interference. General hospital psychiatry. 2018;50:38-44.

15. Mosshammer D, Schaeffeler E, Schwab M, et al. Mechanisms and assessment of statin-related muscular adverse effects. Br J Clin Pharmacol. 2014;78:454-66.

16. Skottheim IB, Gedde-Dahl A, Hejazifar S, et al. Statin induced myotoxicity: the lactone forms are more potent than the acid forms in human skeletal muscle cells in vitro. European Journal of Pharmaceutical Sciences. 2008;33:317-25.

17. Hermann M, Bogsrud MP, Molden E, et al. Exposure of atorvastatin is unchanged but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy. Clinical pharmacology and therapeutics. 2006;79:532-9.

18. Skottheim IB, Bogsrud MP, Hermann M, et al. Atorvastatin metabolite measurements as a diagnostic tool for statin-induced myopathy. Molecular diagnosis & therapy. 2011;15:221-7.

19. Schirris TJ, Renkema GH, Ritschel T, et al. Statin-Induced Myopathy Is Associated with Mitochondrial Complex III Inhibition. Cell metabolism. 2015;22:399-407.

20. Vethe NT, Munkhaugen J, Andersen M, et al. A method for direct monitoring of atorvastatin adherence in cardiovascular disease prevention: Quantification of the total exposure to parent drug and major metabolites using two-channel chromatography and tandem mass spectrometry. Therapeutic Drug Monitoring. 2018(Manuscript in press).

21. Van Vleet TR, Liu H, Lee A, et al. Acyl glucuronide metabolites: Implications for drug safety assessment. Toxicology letters. 2017;272:1-7.

22. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. Circulation. 2013;127:96-103.

23. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients-the PRIMO study. Cardiovascular drugs and therapy. 2005;19:403-14.

24. Chodick G, Shalev V, Gerber Y, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clin Ther. 2008;30:2167-79.

25. McGowan MP. There is no evidence for an increase in acute coronary syndromes after short-term abrupt discontinuation of statins in stable cardiac patients. Circulation. 2004;110:2333-5.

26. Jernberg T, Hasvold P, Henriksson M, et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J. 2015;36:1163-70.

27. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Annals of emergency medicine. 2001;38:633-8.

28. Odessey results. Accessed May 25th 2018 at https://accscientificsession.acc.org/

29. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. The New England Journal of Medicine. 2017;377:1119-31.

Appendices

Figure 1 Study flowchart of the randomized controlled study

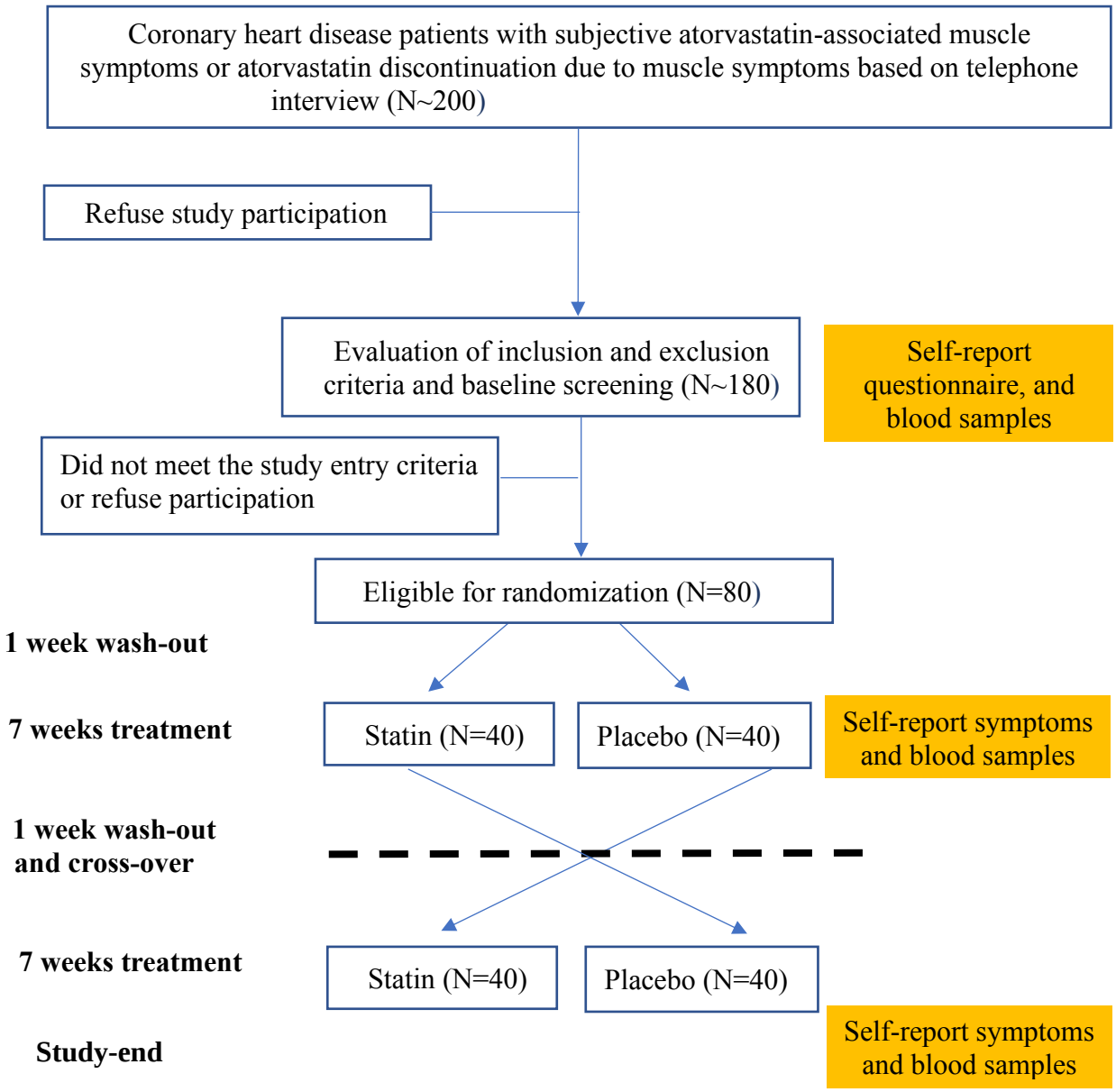

Table 1 Study objectives and related end-points

	Objectives	Endpoints	Assessments
Primary	Estimate the effect of atorvastatin on muscular symptom intensity in CHD patients with subjective SAMS.	Individual difference in muscular symptom intensity between treatment periods with atorvastatin and placebo.	Patient self-report measured with aggregated scores on a 1-10 VAS scale
Secondary	Muscle symptoms on atorvastatin treatment compared with on placebo	Proportion who report muscle symptoms on atorvastatin treatment and not on placebo (dichotomous SAMS classification)	Patient self-report measured with aggregated scores on a 1-10 VAS scale
	The relationship between muscular symptom intensity and blood concentrations of parent drug and the primary metabolites of atorvastatin	The correlation between individual mean difference in muscular symptom intensity between treatment periods and levels of atorvastatin and its metabolites in blood plasma and white blood cells	Patient self-report measured with aggregated scores on a 1-10 VAS scale. Drug and metabolites in blood measured with liquid chromatography-tandem mass spectrometry
	The diagnostic properties of blood concentrations of atorvastatin metabolites for classification of true SAMS	Sensitivity, specificity, and area under the ROC curve of atorvastatin metabolites concentrations for the classification of true SAMS	Patient self-report measured with aggregated scores on a 1-10 VAS scale. Drug and metabolites in blood measured with liquid chromatography-tandem mass spectrometry
	The likelihood of statin discontinuation within and between the treatment periods	Individual mean difference in likelihood of drug discontinuation between treatment periods with statin and placebo.	Patient self-report measured with aggregated scores on a 1-10 VAS scale
	Statin adherence between the two study arms	The proportion with low statin adherence measured with indirect and direct methods	*Indirect methods*: Self-reported questionnaires and pill counts of returned packages, *Direct methods*: Atorvastatin plus metabolites concentration measured by a liquid chromatography-tandem mass spectrometry method
	Atorvastatin and metabolites concentration between patients with failing placebo-test for connecting SAMS to atorvastatin and the control group without muscle symptoms.	Levels of atorvastatin and its metabolites in blood plasma and white blood cells	Drug and metabolites in blood measured with liquid chromatography-tandem mass spectrometry
Explorative	Muscle symptom characteristics in patients with and without confirmed SAMS	The proportion who report muscle symptoms on atorvastatin treatment and not on placebo (dichotomous SAMS)	Patient self-report measured with McGill Pain Questionnaire and Brief Pain Inventory

	Objectives	Endpoints	Assessments
	Sociodemographic, clinical, and psychosocial characteristics between the two study arms	The proportion who report muscle symptoms on atorvastatin treatment and not on placebo (dichotomous SAMS)	Obtained through self-reported questionnaires, clinical examinations, and blood samples

Table 2 Enrollment criteria

Inclusion criteria (all the following)

- First or recurrent CHD event (i.e. myocardial infarction, and/or coronary revascularization) at least 6months prior to study start and prescribed atorvastatin.
- Self-reported muscle complaints attributed to atorvastatin therapy or atorvastatin discontinuation due to muscle complains**
- Age >18 years and signed informed consent

Exclusion criteria (any of the following)

- A CHD event the past 12 months prior to study start in *high-risk* patients (i.e. systolic heart failure, >1 previous myocardial infarction, kidney failure, diabetes, and smokers) and the past 6 months prior to study start in patients non high-risk patients and in patients not taking a statin at all
- Residual non-revascularized stenosis on the major coronary arteries, symptomatic peripheral artery disease and familial hypercholesterolemia
- Any contraindications for atorvastatin listed in the Summary of Product Characteristics
- History of rhabdomyolysis, myopathy or liver failure due to statin treatment or creatine kinase > 10 times upper limit of the normal range or Alanine aminotransferase >3 times upper limit of the normal range at baseline
- Any condition or situation, that could put the subject at significant risk, confound the study results or rendering informed consent unfeasible
- Short life expectancy
- Not being able to understand Norwegian.
- Women of childbearing potential
- Participation in another randomized trial

**Reporting subjective muscle symptoms during atorvastatin treatment or discontinuation due to muscle symptoms is an enrollment criterion for the randomized controlled study group (n=80) only, whereas a prerequisite for participation in the control group (n=40) is no history of perceived SAMS and no other ongoing muscle symptoms. The other enrollment criteria are similar for the two groups.

Table 3 Study data collection

	The randomized controlled study group (N=80)				**Control group (N=40)**
	Telephone screening (n~180)	**Baseline evaluation (n=80)**	**Two x 7-weeks treatment period (n=80)**	**Study-end**	
Inclusion/exclusion evaluation[1)]	X	X			X
Informed consent and randomization[2)]		X			X
Collection of relevant hospital record data[3)]		X			X
Self-reported questionnaires (PROMs)[4)]		X	X	X	X
Collection of blood samples[5)]		X	X*		X
Safety assessment [6)]		X	X		

1. Inclusion/exclusion evaluation will be performed by study physicians.
2. Randomization and collection of informed consent performed by study physician.
3. Relevant hospital record data registered by study nurses: Age, gender, ethnicity, medical history and treatment including statin type and doses, and adverse statin reactions
4. The self-report questionnaire comprises current and previous statin treatment, discontinuation,/dose reduction and adherence, lifestyle behaviour (smoking history, physical activity, body weight and height), Beliefs about medicines questionnaire muscle symptoms (i.e. pain/aching, stiffness, tenderness or cramps) and characteristics (short-form McGill Pain Questionnaire and Brief Pain Inventory)), psychosocial factors (the Hospital Anxiety and Depression Scale, the Patient Health Questionnaire-2), Distress Scale-14 questionnaire, Penn State Worry Questionnaire, Bergen Insomnia scale), and quality of life (Short Form-12). Muscle symptoms and likelihood of statin discontinuation will be measured on Visual Analogue Scales and Numeric Rating Scales weekly during the treatment periods.
5. Blood tests: HbA1c, hemoglobin, hs-C-Reactive Protein, creatinine, creatine kinase, alanine aminotransferase , total protein, albumin, total cholesterol, HDL cholesterol, LDL cholesterol and pharmacogenetic variants in SLCO1B1 and CYP3A. Blood concentrations of atorvastatin and metabolites (e.g. atorvastatin acid, atorvastatin lactone, atorvastatin 4-hydroxy [OH] lactone and acid, and atorvastatin 2-hydroxy [OH] lactone and acid plus reactive acylglucuronide) in plasma and in white blood cells (i.e. lymphocytes).
6. Safety data will be collected at baseline, at the end of each treatment period and from telephone interviews.