


BMJ Open Tolerability of statin-based management of patients with a history of statin-associated muscle symptoms: protocol for a systematic review

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ABSTRACT

Introduction Statin-associated muscle symptoms (SAMSs) are a major clinical issue in the primary and secondary prevention of cardiovascular events. Current guidelines advise various approaches mainly based on expert opinion. We will lead a systematic review and meta-analysis to explore the tolerability and acceptability and effectiveness of statin-based therapy management of patients with a history of SAMS. We aim to provide evidence on the tolerability and different strategies of statin-based management of patients with a history of SAMS.

Methods and analysis We will conduct a systematic review of randomised controlled trials (RCTs) and non-randomised studies with a control group. We will search in Data sources MEDLINE, EMBASE, Cochrane Central Register of Controlled Clinical Trials, Scopus, Clinicaltrials.gov and Proquest from inception until April 2021. Two independent reviewers will carry out the study selection based on eligibility criteria. We will extract data following a standard data collection form. The reviewers will use the Cochrane Collaboration's tools and Newcastle-Ottawa Scale to appraise the study risk of bias. Our primary outcome will be tolerability and our secondary outcomes will be acceptability and effectiveness. We will conduct a qualitative analysis of all included studies. In addition, if sufficient and homogeneous data are available, we will conduct quantitative analysis. We will synthesise dichotomous data using OR with 95% CI and continuous outcomes by using mean difference or standardised mean difference (with 95% CI). We will determine heterogeneity visually with forest plots and quantitatively with I^2 and Q-test. We will summarise the confidence in the quantitative estimate by using Grading of Recommendations Assessment, Development and Evaluation approach.

Ethics and dissemination As a systematic review of literature without collection of new clinical data, there will be no requirement for ethical approval. We will disseminate findings through peer-reviewed publications.
PROSPERO registration number CRD42020202619.

INTRODUCTION

Statin-associated muscle symptoms (SAMSs), a composite of muscle symptoms appearing consequent to the initiation or the increase

Strengths and limitations of this study

- This systematic review protocol observes the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols checklist.
- This systematic review will be the first to systematically review tolerability of statin-based management in patients with a history of statin-associated muscle symptom.
- This systematic review will provide the highest level of evidence for clinical decisiveness due to the inclusion of randomised controlled trials (RCTs) as well as non-RCTs.
- Heterogeneity of the studies may not permit a quantitative analysis.

of a statin's treatment,¹ are a major clinical issue in the primary and secondary prevention of cardiovascular events. Statins are a cornerstone in the prevention of cardiovascular risk and mortality,^{2 3} and are widely prescribed with increased intensity to achieve currently recommended low-density lipoprotein cholesterol (LDL-C) levels.⁴⁻⁶ Nevertheless, SAMS, a commonly reported muscle symptom, threatens the ability of a significant proportion of patients to tolerate evidence-based dosing: based on observational data or registries reported by patients. SAMS affects between 5% and 29% of statin-treated individuals.¹ This lack of tolerability is associated with higher cardiovascular disease risk.⁶ Meanwhile, the high cost of the non-statin alternative drugs, such as PCSK9 inhibitors, and the lack of other effective alternatives, remains a concern,^{7 8} and statins currently remain the main treatment option.

The European Atherosclerosis Society Consensus Panel Statement recommend multiple different strategies to manage patients with SAMS but they are based only on experts' opinion due to lack of sufficient data.¹

A systematic review and meta-analysis of 12 randomised controlled trials (RCTs) and one quasi-RCT on the efficacy and safety of alternate day versus daily dosing of statins with participants without previous SAMS in 2017 found a statistically non-significant difference in terms of change in LDL-C in both groups and concluded good adherence and tolerability of both treatment.⁹ However, this meta-analysis has not assessed the specific population of patients suffering from SAMS. A systematic review of three case reports, five retrospective studies, one prospective study and one randomised trial assessing effectiveness of intermittent non-daily administration of statin strategies with patients with previous statin-induced myopathy in 2013 found that 70% of patients could tolerate an intermittent dosing strategy and concluded that uncertainty remains and that larger scale randomised trials are required.¹⁰

Since publication of these systematic reviews, new evidence on the management of SAMS has emerged both from RCTs and observational data.¹¹⁻¹⁶ Therefore, we decided to conduct a systematic review and meta-analysis to investigate the tolerability, acceptability and effectiveness of statin-based therapy management in patients with a history of SAMS compared with all available comparators. In a patient-centred perspective, we will focus on the tolerability as the primary outcome. We will not only include intermittent dosing strategies, but also other strategies to broaden our conclusion. Our systematic review and meta-analysis will be complementary to the ongoing meta-analysis¹⁷ on statin adverse events with the particularity to focus on patients with a history of SAMS and SAMS' management.

We aim to provide quality evidence for the tolerability of statin-based management of patients with a history of SAMS. We will also highlight gaps in available evidence to direct further research.

METHODS AND ANALYSIS

Eligibility criteria

Types of studies

We will include human RCTs and prospective and retrospective cohort studies with a control group, published in English from inception until April 2021. There will be no follow-up length or setting restriction. We will include relevant studies mainly based on the population and intervention criteria to avoid exclusion of studies which poorly report tolerability or adverse outcomes in their titles and abstracts. In the case of multiple publications from the same study, we will include the report with the most relevant data relating to our interest.

We will differentiate between the absence of muscle symptoms and the absence of reporting muscle symptoms and include data only from studies reporting the absence of muscle symptoms. We will include post-hoc analysis of prior RCT so long as there is a comparison group.

Types of participants

We will include studies examining adult humans previously on statins with a history of SAMS. We will also include studies examining adults previously on statins with a history of statin intolerance without precision of SAMS or other intolerance. Indeed, SAMS is a type of statin intolerance concerning specifically muscle symptoms. Nevertheless, some participants can also report other types of intolerance, as for example, impaired cognition,¹⁸ hepatic dysfunction¹⁹ or depression.²⁰ SAMS is also a recent definition and could have been reported as 'intolerance' or 'muscle-related adverse events' in the past.

We will exclude studies examining adults without a history of statin intolerance, children, adolescents and pregnant women.

Types of interventions

We defined statin-based therapy management of patients with a history of SAMS as all statin management strategies with the aim of optimal lipid profile lowering and decreasing adverse effects. Examples include statin continuation, re-challenge, up-titration, down-titration, second statin at the usual or starting dose, low dosing of a high-intensity statin, intermittent dosing statin. All the variations of statin management strategies will be included, for example the variation in dosage, intensity, frequency of delivery, duration of delivery and timing of delivery. All co-lifestyle modifications (exercise and diet) and all additional interventions in the intervention group are included if present in the control group too.

Types of comparators

Placebo, usual care, other statins regimens, other non-statin lipid-lowering drug regimens (ezetimibe, PCSK9 inhibitors), statin regimens with additional interventions (statins with ezetimibe, CoQ10, vitamin D) or no treatment.

Types of outcomes

Tolerability, as defined in individual studies, will be our main outcome. We anticipate that the proportion of population with muscle symptoms-related adverse events compared with control group would be the most feasible measure to analyse. If reported, we will collect time until muscle symptoms-related adverse events and measure the adverse event rate.

We defined adverse event as 'an unfavorable outcome that occurs during or after the use of a drug or other intervention and the causal relation between the intervention and the event is at least a reasonable possibility' as defined in the *Cochrane handbook for systematic reviews of interventions*.²¹

Acceptability, as defined in individual studies, will be a secondary outcome. We anticipate that the proportion of population with muscle symptoms-related study or treatment discontinuation compared with control group will be the most feasible measure to analyse.

Effectiveness, defined as the change in lipid profile will be a secondary outcome. The lipid profile includes at least LDL-C in addition to total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides as provided by the individual studies.

Search strategy and study selection

Search strategy

The first author will develop a search strategy for each database included MEDLINE, EMBASE and Cochrane Central Register of Controlled Clinical Trials in cooperation with a trained librarian using computerised search (see online supplemental file 1). Search terms and syntax will be adapted for each specific database. Moreover, we will complete a hand search using forward and backwards citations, and evaluate the grey literature (Scopus, Clinicaltrials.gov and Proquest) for additional potentially relevant and unpublished articles. We will search only studies written in English.

Study selection

Two trained reviewers (FV and CL) will evaluate independent eligibility based on titles and abstracts of all studies retrieved in our electronic search.²¹ We will upload the literature search results to Rayyan QCRI, an internet-based software programme that facilitates collaboration among reviewers during the selection process. We will remove duplicates using reference management software. The two reviewers will assess the remaining studies for inclusion after full-text evaluation. If studies do not report muscle symptoms events or discontinuation in the full text, we will request them from the authors. We will then

include or exclude the study, depending on the information provided. We will still include studies with absence of reporting muscles symptoms if they present data of interest for secondary outcomes. We will include post-hoc analysis of prior RCT so long as there is a comparison group.

We will list excluded full-text studies together with the reason for exclusion. We will resolve discrepancies by making a consensus among the study team. If we cannot reach consensus, we will consult a third reviewer. We will follow the Preferred Reporting Items for Systematic Review and Meta-Analyses recommendations to summarise the study selection. We will document all decisions made in the study selection process.

Data extraction and management

We will manage data with an online shared data form among the review team.

We will use a standard data collection form, piloted by the review team using representative sample of included studies. Two reviewers will manage data in duplicate. We will request additional data from the authors by email. The two reviewers will discuss and resolve disagreements by consensus or consult a third reviewer.

The data collection items are listed in [table 1](#).

Quality assessment

Two reviewers will autonomously evaluate the risk of bias of each study. We will use the Cochrane Collaboration tools for appraising the risk of bias of prospective studies and the Newcastle-Ottawa scale for the retrospective

Table 1 Data collection items

General	▶ Authors, journal, year of publication, title of the article.
Method	▶ Study design. ▶ Participants. ▶ Sample size, loss to follow-up. ▶ Characteristics of participants at baseline as age, sex, body mass index, cardiovascular comorbidities, cardiovascular risk factors, co-medications with influence on the cytochrome of interest, history of adverse reaction to multiple medications, lipid profile, past achievement of LDL-C goals; creatine kinase, liver function test, intolerance, SAMS.
Intervention and control	▶ Statins, doses, timing, frequency, length of intervention, washout period, duration of follow-up. ▶ Description of co-interventions, lifestyle modification, modification of baseline medication regimen. ▶ Types of comparator, doses, timing, frequency, intervention protocols, length of intervention, washout period, duration of follow-up.
Outcomes	▶ Proportion of population with/without muscles symptoms-related adverse events, time to muscles symptoms-related adverse events, proportion of population with muscles symptoms related drop out, lipid profile, creatine kinase level, liver function test. ▶ Multiple adverse events occurrence in the same individuals. ▶ All other adverse outcomes and collection systematic: definition of each adverse outcome addressed, method of ascertainment (patient report vs active search), method of measurement, timing and frequency of adverse events, measurement of the severity. ▶ Associated factor to the adverse events. ▶ For each outcome at each time point: number of participants randomly assigned and included in the analysis; number of participants who withdrew, were lost to follow-up or were excluded with reasons for each.
Notes	▶ Conflicts of interest, funding sources.

SAMS, statin-associated muscle symptom.

studies. Discrepancy among the two reviewers will be solved by consensus or by a third person.

On the meta-bias level, a sensitivity analysis to determine the effect of selective reporting will also be considered. If data permits, we will assess small study effect via funnel plots and formally with the Egger test.

Data synthesis and statistical analyses

We will synthesise the systematic review qualitatively and quantitatively.

In the qualitative synthesis, we will summarise the characteristics and findings of the included studies in text and tables. We will categorise our summaries of studies according to type of intervention, comparator, outcome and study design. We will present the limitations of the included studies and recommendations for future research.

In the quantitative synthesis, we will perform study level meta-analysis if studies are sufficiently homogenous and if enough data are available.

We will use the same summary measures in RCT and non-randomised trials. For tolerability and acceptability, we will synthesise dichotomous data using OR with 95% CI. For efficacy, we will synthesise the change in lipid profile from baseline as a continuous outcome using mean difference or standardised mean difference (with 95% CI) depending on the different metrics.

When studies reported the number of muscle events instead of the number of subjects experiencing muscular event, we will contact the authors to request the number of patients with >0 events. If this could not be addressed, we will make the assumption of one event per subject. If a group of the studies reported zeroes event, we will use the zero count-cell method to allow statistical measures. We will exclude studies with zero events in both groups from the analysis.

Concerning acceptability, if the measure to analyse is the proportion of population with muscle symptoms-related discontinuation compared with the control group, we will assess if the participant was still blinded to treatment attribution before the discontinuation to avoid bias.

Regarding the variety of study designs, we will first pool data, then analyse data from different type of studies separately (eg, RCT vs non-randomised control studies, crossover trial vs parallel trial). We will collect the variables used for the adjustment in each study. When dealing with crossover trials, data after the crossover will be analysed.

We will assess heterogeneity visually with forest plots, I^2 test and the Q -test. We will assess and interpret heterogeneity in line with the guidance in the *Cochrane handbook of systematic reviews and meta-analysis*. In case of heterogeneity, we will explore potential sources in subgroup analyses. In the case of significant heterogeneity, we will use the random effect model.

We will conduct subgroup analysis to explore possible sources of heterogeneity: pre-planned variables to explore are primary versus secondary prevention, high intensity versus non-high intensity statins, intermittent dosing

versus daily dosing, patients with a history of SAMS versus patients with a history of statin intolerance, only statins intervention versus statins and additional interventions and participants with versus without a statin at inclusion. If feasible, we will consider the different follow-up times in a meta-regression.

We will conduct the analysis using STATA V.16 software (StataCorp, College Station, Texas, USA).

We will recapitulate the confidence we have in the resulting body of evidence using Grading of Recommendations Assessment, Development and Evaluation working group methodology.

ETHICS AND DISSEMINATION

We plan to publish the review in a clinical journal from the relevant field (endocrinology, cardiology and internal medicine).

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design or conduct or reporting or dissemination plans of this research.

Acknowledgements We thank Miss Tania Rivero, medical information specialist from the University of Bern for her help in developing the search strategy.

Contributors FV, MB and NR designed the topic. FV carried out background exploratory searches. FV elaborated the search strategy. FV wrote the protocol. MB, CDG and NR gave critical appraisal and senior control. For the systematic review, FV and LC will accomplish the searches, data extraction and risk of bias assessment. FV will execute the analysis. MB will supervise the searches, data analysis and extraction. CDG will supply statistical expertise for data analysis. All authors have approved the publication of the protocol after cautious reading.

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Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

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1 **Supplementary file**2 **PRISMA-P Checklist**

Section and topic	Item No	Checklist item	Information reported	Line number(s)
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	45
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	8-15
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	307-311
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes	320-321
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	312-313
Sponsor	5b	Provide name for the review funder and/or sponsor	NA	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA	
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	62-95
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	96-98
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	100-205
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	208-214
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes	Supplementary file 12-18
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	231-237
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes	215-226
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	232-237
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	Table 1

Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	191-205 and Table 1
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	238-242
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	257-258
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	Yes	259-281
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes	282-287
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	253-256
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes	248-250
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	296-298

3 *** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P**
4 **Explanation and Elaboration (cite when available) for important clarification on the items.**
5 **Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P**
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7 **Commons Attribution Licence 4.0.**

8 *From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L,*
9 *PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols*
10 *(PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

11 Search strategy

Data search strategy for embase.com

#	Searches	
#1	'antilipemic agent'/exp	
#2	'anticholesteremic':ab,kw,ti,tn OR 'antihypercholesteremic':ab,kw,ti,tn OR 'altacor':ab,kw,ti,tn OR 'atorvastatin':ab,kw,ti,tn OR 'baycol':ab,kw,ti,tn OR 'bervastatin':ab,kw,ti,tn OR 'canef':ab,kw,ti,tn OR 'cerivastatin':ab,kw,ti,tn OR 'compactin':ab,kw,ti,tn OR 'cranoc':ab,kw,ti,tn OR 'crestor':ab,kw,ti,tn OR 'crilvastatin':ab,kw,ti,tn OR 'dalvastatin':ab,kw,ti,tn OR 'fluidostatin':ab,kw,ti,tn OR 'fluvastatin':ab,kw,ti,tn OR 'glenvastatin':ab,kw,ti,tn OR 'hmg coa':ab,kw,ti,tn OR 'hydroxymethylglutaryl':ab,kw,ti,tn OR 'hypocholesterol':ab,kw,ti,tn OR 'hypolipidemic':ab,kw,ti,tn OR 'lescol':ab,kw,ti,tn OR 'lipitor':ab,kw,ti,tn OR 'lipex':ab,kw,ti,tn OR 'lipostat':ab,kw,ti,tn OR 'livalo':ab,kw,ti,tn OR 'local':ab,kw,ti,tn OR 'lovostatin':ab,kw,ti,tn OR 'lochol':ab,kw,ti,tn OR 'medostatin':ab,kw,ti,tn OR 'mevacor':ab,kw,ti,tn OR 'mevalotin':ab,kw,ti,tn OR 'mevinacor':ab,kw,ti,tn OR 'mevinolin':ab,kw,ti,tn OR 'monacolin':ab,kw,ti,tn OR 'pitava':ab,kw,ti,tn OR 'pitavastatin':ab,kw,ti,tn OR 'pravachol':ab,kw,ti,tn OR 'pravasin':ab,kw,ti,tn OR 'pravastatin':ab,kw,ti,tn OR 'rosuvastatin':ab,kw,ti,tn OR 'simvastatin':ab,kw,ti,tn OR 'zocor':ab,kw,ti,tn OR 'statin':ab,kw,ti,tn	Statins
#3	#1 OR #2	
#4	'muscle disease'/exp	
#5	((muscl* OR muscu*) NEAR/3 (pain* OR fatigue OR intoler* OR symptom*)):ti,ab,kw) OR ((statin* NEAR/3 (induc* OR relat* OR associ* OR intoler* OR symptom* OR side effect* OR side-effect* OR adverse effect*)):ti,ab,kw) OR sams:ti,ab,kw OR sas:ti,ab,kw OR sinam:ti,ab,kw OR myopath*:ti,ab,kw OR myalg*:ti,ab,kw OR myosit*:ti,ab,kw OR necrot*:ti,ab,kw OR rhabdomyo*:ti,ab,kw	SAMS
#6	#4 OR #5	
#7	#3 AND #6	
#8	'dosage schedule comparison'/exp OR 'drug choice'/exp OR 'drug dose comparison'/exp OR 'drug dose escalation'/exp OR 'drug dose increase'/exp OR 'drug dose intensification'/exp OR 'drug dose reduction'/exp OR 'drug dose regimen'/exp OR 'drug dose titration'/exp OR 'drug intermittent therapy'/exp OR 'drug megadose'/exp OR 'drug microdose'/exp OR 'drug pulse therapy'/exp OR 'low drug dose'/exp OR 'loading drug dose'/exp OR 'maintenance drug dose'/exp OR 'recommended drug dose'/exp OR 'optimal drug dose'/exp	Managements
#9	((daily OR everyday OR quotidian OR 'every other' OR 'every second' OR rotat* OR alternat* OR 'non daily' OR nondaily OR non-daily OR hebdomad* OR weekly OR intermit* OR escalat* OR build-up OR intensif* OR reduct* OR puls*) NEAR/3 (therap* OR dos* OR treatment OR prescript*)):ti,ab,kw) OR reinitation:ti,ab,kw OR challeng*:ti,ab,kw OR rechalleng*:ti,ab,kw OR 're challeng*':ti,ab,kw OR monotherap*:ti,ab,kw	
#10	#8 OR #9	
#11	#7 AND #10	
#12	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	RCT
#13	cohort:ab,ti OR (case:ab,ti AND (control:ab,ti OR controll*:ab,ti OR comparison:ab,ti OR referent:ab,ti)) OR risk:ab,ti OR causation:ab,ti OR causal:ab,ti OR 'odds ratio':ab,ti OR etiol*:ab,ti OR aetiol*:ab,ti OR 'natural history':ab,ti OR predict*:ab,ti OR prognos*:ab,ti OR outcome:ab,ti OR course:ab,ti OR retrospect*:ab,ti OR 'epidemiology'/de	Observational studies
#14	#12 OR #13	
#15	#11 AND #14	

Filter: <https://blocks.bmi-online.nl/catalog/106>

Creator: Ket JCF and Vries R de

Notes: PubMed drafted in 2009 from: Etiology, causation, harm; and: Natural history and prognosis. In: McKibbin KA, Eady A, Marks S. PDQ evidence-based principles and practice. Hamilton etc.: B.C. Decker; 1999, p. 91, 110. PubMed revised in 2015 by adding '[ot]'. Embase.com drafted by De Vries, 2015. PubMed and Embase.com for non-randomized and observational designs from: <http://guides.library.harvard.edu/c.php?g=309982&p=2079546> (Countway Library of Medicine, 31 Aug 2016).

Date: 2016-08-31

University Library Vrije Universiteit Amsterdam

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Data search strategy for Ovid Medline®

#	Searches	
1	exp hypolipidemic Agents/ (Anticholesteremic or antihypercholesteremic or altacor or atorvastatin or baycol or bervastatin or canef or cerivastatin or compactin or cranoc or crestor or crilvastatin or dalvastatin or fluidostatin or fluvastatin or glenvastatin or hmg coa* or hydroxymethylglutaryl* or hypocholesterol* or hypolipidemic* or lescol or lipitor or lipex or lipostat or livalo or local or lovostatin or lochol or medostatin or mevacor or mevalotin or mevinacor or mevinolin or monacolin or pitava or pitavastatin or pravachol or pravasin or pravastatin or rosuvastatin or simvastatin or zocor or statin*).ab,kw,ti,nm.	Statins
2	1 or 2	
3	exp muscular diseases/	
4	((muscl* or muscu*) adj3 (pain* or fatigue or intoler* or symptom*)) or (statin* adj3 (induc* or relat* or associ* or intoler* or symptom* or side effect* or side-effect* or adverse effect*)) or sams or sas or sinam or myopath* or myalg* or myosit* or necrot* or rhabdomyo*).ti,ab,kw.	SA
5	4 or 5	
6	3 and 6	
7	exp drug therapy/	^

3

9 (((daily or everyday or quotidian or every other or every second or rotat* or alternat* or non daily or nondaily or non-daily or hebdomad* or weekly or intermit* or escalat* or build-up or intensif* or reduct* or puls*) adj3 (therap* or dos* or treatment or prescript*)) or reinitiation or challeng* or rechalleng* or re challeng* or monotherap*).ab,kw,ti.

10	8 or 9	
11	7 and 10	
12	Randomized controlled trial.pt.	RCT
13	controlled clinical trial.pt.	
14	Randomi?ed.ab.	
15	placebo.ab.	
16	drug therapy.fs.	
17	randomly.ab.	
18	trial.ab.	
19	groups.ab.	
20	or/12-19	
21	exp animals/ not humans.sh.	
22	20 not 21	
23	Epidemiologic studies/	Observational studies
24	exp case control studies/	
25	exp cohort studies/	
26	Case control.tw.	
27	(cohort adj (study or studies)).tw.	
28	Cohort analy\$.tw.	
29	(Follow up adj (study or studies)).tw.	
30	(observational adj (study or studies)).tw.	
31	Longitudinal.tw.	
32	Retrospective.tw.	
33	Cross sectional.tw.	
34	Cross-sectional studies/	
35	or/23-34	
36	22 or 35	
37	11 and 36	

Filters

https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies#_Ref19195060
<https://www.sign.ac.uk/what-we-do/methodology/search-filters/>

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Database search strategy for Cochrane library

#	Searches	
#1	(Anticholesteremic or antihypercholesteremic or altocor or atorvastatin or baycol or bervastatin or canef or cerivastatin or compactin or cranoc or crestor or crivastatin or dalvastatin or fluintostatin or fluvastatin or glenvastatin or hmg coa* or hydroxymethylglutaryl* or hypochol* or hypolipidemic* or lescol or lipitor or lipex or lipostat or livalo or locol or lovostatin or lochol or medostatin or mevacor or mevalotin or mevinacor or mevinolin or monacolin or pitava or pitavastatin or pravachol or pravasin or pravastatin or rosuvastatin or simvastatin or zocor or statin*);ti,ab, kw	Statins
#2	(((muscl* OR muscu*) NEAR/3 (pain* OR fatigue OR intoler* OR symptom*)) OR ((statin* NEAR/3 (induc* OR relat* OR associ* OR intoler* OR symptom* OR "side effect" OR side-effect* OR "adverse effect")) OR sams OR sas OR sinam OR myopath* OR myalg* OR myosit* OR necrot* OR rhabdomyo*));ti,ab,kw	SAM
#3	#1 AND #2	
#4	(((daily or everyday or quotidian or "every other" or "every second" or rotat* or alternat* or "non daily" or nondaily or non-daily or hebdomad* or weekly or intermit* or escalat* or build-up or intensif* or reduct* or puls*) near/3 (therap* or dos* or treatment or prescript*)) or reinitiation or challeng* or rechalleng* or "re challeng*" or monotherap*).ab,kw,ti.	Managements
#5	#1 AND #2 AND #4	

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Database search strategy for Scopus

Searches

4

15 TITLE-ABS-KEY (anticholesteremic OR antihypercholesteremic OR altacor OR atorvastatin OR baycol OR bervastatin OR canef OR cervastatin OR compactin OR cranoc OR crestor OR crilvastatin OR dalvastatin OR fluindostatin OR fluvastatin OR glenvastatin OR "hmg coa*" OR hydroxymethylglutaryl* OR hypochole* OR hypolipidemic* OR lescol OR lipitor OR lipex OR lipostat OR livalo OR local OR lovostatin OR lochol OR medostatin OR mevacor OR mevalotin OR mevinacor OR mevinolin OR monacolin OR pitava OR pitavastatin OR pravachol OR pravasin OR pravastatin OR rosuvastatin OR simvastatin OR zocor OR statin*) AND TITLE-ABS-KEY (((muscl* OR muscu*) W/3 (pain* OR fatigue OR intoler* OR symptom*)) OR ((statin* W/3 (induc* OR relat* OR associ* OR intoler* OR symptom* OR "side effect*" OR side-effect* OR "adverse effect*"))) OR sams OR sas OR sinam OR myopath* OR myalg* OR myosit* OR necrot* OR rhabdomyo*)) AND TITLE-ABS-KEY (((daily OR everyday OR quotidian OR "every other" OR "every second" OR rotat* OR alternat* OR "non daily" OR nondaily OR non-daily OR hebdomad* OR weekly OR intermit* OR escalat* OR build-up OR intensif* OR reduct* OR puls*) W/3 (therap* OR dos* OR treatment OR prescript*)) OR reinitiation OR challeng* OR rechalleng* OR "re challeng*" OR monotherap*)

Database search strategy for Clinicaltrials.gov

Searches

16 1 (atorvastatin OR fluvastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin OR statin) AND (pain OR fatigue OR intolerance OR symptom OR side OR adverse OR myopathy OR myalgia OR myositis OR rhabdomyolysis OR muscular OR muscle)

Datadbse search strategy for Proquest

Searches

17 1 AB,TI,IF(anticholesteremic OR antihypercholesteremic OR altacor OR atorvastatin OR baycol OR bervastatin OR canef OR cervastatin OR compactin OR cranoc OR crestor OR crilvastatin OR dalvastatin OR fluindostatin OR fluvastatin OR glenvastatin OR "hmg coa*" OR hydroxymethylglutaryl* OR hypochole OR hypolipidemic OR lescol OR lipitor OR lipex OR lipostat OR livalo OR local OR lovostatin OR lochol OR medostatin OR mevacor OR mevalotin OR mevinacor OR mevinolin OR monacolin OR pitava OR pitavastatin OR pivastatin OR pravachol OR pravasin OR pravastatin OR rosuvastatin OR simvastatin OR zocor OR statin*) AND AB,TI,IF(muscl* OR muscul* OR pain* OR fatigue OR intoler* OR symptom* OR SAMS OR SAS OR SINAM OR rhabdomyo* OR myosit* OR myopath* OR myalg* OR necrot*)