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Prevalence of statin intolerance: a meta-analysis.

Prevalence of Statin Intolerance: a meta-analysis

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ABSTRACT

Aims: Statin intolerance (SI) represents a significant public health problem for which precise estimates of prevalence are needed. SI remains an important clinical challenge, and it is associated with an increased risk of cardiovascular events. This meta-analysis estimates the overall prevalence of SI, the prevalence according to different diagnostic criteria and in different disease settings, and identifies possible risk factors/conditions that might increase the risk of SI.

Methods and results: We searched several databases up to 31st May 2021, for studies that reported the prevalence of SI. The primary endpoint was overall prevalence and prevalence according to a range of diagnostic criteria [National Lipid Association (NLA), International Lipid Expert Panel (ILEP) and European Atherosclerosis Society (EAS)] and in different disease settings. The secondary endpoint was to identify possible risk factors for SI. A random-effects model was applied to estimate the overall pooled prevalence. A total of 176 studies [112 randomized controlled trials (RCTs); 64 cohort studies] with 4,143,517 patients were ultimately included in the analysis. The overall prevalence of SI was 9.1% [95% confidence interval (CI) 8.0-10%]. The prevalence was similar when defined using NLA, ILEP and EAS criteria [7.0 (6.0-8.0%), 6.7 (5.0-8.0%), 5.9% (4.0-7.0%), respectively]. The prevalence of SI in RCTs was significantly lower compared with cohort studies [4.9 (4.0-6.0%) vs 17% (14-19%)]. The prevalence of SI in studies including both primary and secondary prevention patients was much higher than when primary or secondary prevention patients were analyzed separately [18 (14-21%), 8.2 (6.0-10%), 9.1% (6.0-11%), respectively]. Statin lipid solubility did not affect the prevalence of SI [4.0 (2.0-5.0%) vs 5.0% (4.0-6.0%)]. Age [odds ratio (OR) 1.33, p=0.04], female gender (OR 1.47, p=0.007), Asian and Black race (p<0.05 for both), obesity (OR 1.30, p=0.02), diabetes mellitus (OR 1.26, p=0.02), hypothyroidism (OR 1.37, p=0.01), chronic liver and renal failure (p<0.05 for both) were significantly associated with SI in the meta-regression model. Antiarrhythmic agents, calcium channel blockers, alcohol use and increased statin dose were also associated with higher risk of SI.

Conclusions: Based on the present analysis of >4 million patients, the prevalence of SI is low when diagnosed according to international definitions. These results support the concept that the prevalence of complete SI might often be overestimated and highlight the need for the careful assessment of patients with potential symptoms related to SI.

Key words: cardiovascular disease, prevalence, risk factors, statin intolerance.

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INTRODUCTION

Cardiovascular (CV) disease (CVD) is the leading cause of morbidity and mortality worldwide, despite continuous improvement of medical treatment, diagnosis, and risk factor control [1]. It is has clearly been demonstrated that statin therapy confers significant mortality and morbidity benefits in both the primary and secondary prevention of CVD. [2]. Although statins are among the most commonly prescribed drugs, non-adherence and discontinuation of statin therapy is an ongoing problem worldwide [3]. The most common cause of discontinuation of statin therapy is statin-associated muscle symptoms (SAMS) [4,5]. Other possible statin-related adverse effects include neurocognitive disorders, hepatotoxicity, haemorrhagic stroke and renal toxicity [6,7]. These conditions may lead to discontinuation, but causality has been confirmed only for SAMS, temporary elevation of aminotransferase alanine and newly diagnosed diabetes [6]. According to the International Lipid Panel Expert (ILEP), statin intolerance (SI) is an inability to tolerate a dose of statin required to sufficiently reduce an individual's CV risk, limiting the effective treatment of patients at risk of, or with, CVD [7]. The National Lipid Association (NLA) has a wider definition, including any adverse effects relating to quality of life and leading to the decision to decrease or stop the use of an otherwise beneficial drug [8]. The Luso-Latin American Consortium (LLAC) definition of SI is similar to that of the Canadian Consensus Working Group (CCWG). It refers to an inability to tolerate ≥2 statins at any dose or an inability to tolerate increasing doses. The symptoms must not be attributable to drug-drug interactions or conditions known to increase SI [9,10]. They indicate that symptomatic criteria include intolerable muscle symptoms (pain, weakness, or cramps with or without creatine kinase [CK] changes) or severe myopathy, and they must appear in the first 12 weeks after initiating treatment or following an increase in dose [9,10].

The prevalence of SI is widely debated, in part because of difficulties in identification and diagnosis, possible interaction of different risk factors, different diseases, drugs and other clinical and demographic indices [11]. In contrast with randomized controlled trials (RCTs) (prevalence usually 5-7%), cohort studies suggest that SI occurs in as many as 30% of treated patients [8,12]. However, this is likely to be an overestimate or underestimate and in many cases, the symptoms are likely to be attributable to the nocebo/drucebo effect [11].

Because of these inconsistent findings, the present meta-analysis aimed to estimate the overall prevalence of SI, its prevalence according to various diagnostic criteria, in different disease settings and to identify possible risk factors for SI.

METHODS

Search strategy and selection criteria

We followed the methods recommended by the Cochrane Collaboration and complied with the reporting standards of the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) guideline of 2020. [13]. A PECOS (population, exposure, comparison, outcomes, study design) model was used to shape the clinical question and to design the search strategy (**Table S1**). The following databases were searched from inception through 31st May 2021: PubMed-Medline, EMBASE, Scopus, Google Scholar, the Cochrane Central Registry of Controlled Trials and ClinicalTrial.gov. The following key words were used: statin intolerance, statin toxicity, statin adverse effects, statin side effects, statin-associated muscle symptoms, SAMS, statin-related myopathy, statin-related side effects, statin-related myalgia, statin discontinuation, statin withdrawal, prevalence, occurrence rate and frequency rate (**Table S2**). In addition, the references from the selected articles and from relevant review articles, and the abstracts from selected congresses: scientific sessions of the European Society of Cardiology (ESC), the American Heart Association (AHA), American College of Cardiology (ACC), NLA, and European Atherosclerosis Society (EAS) were screened for additional relevant articles. The wild-card term ‘‘*’’ was used to increase the sensitivity of the search strategy.

Articles were eligible if they reported the prevalence of SI either in primary or secondary prevention and met the following inclusion criteria: 1) trials or cohorts reporting SI, 2) at least 100 participants included in the analysis, and, 3) available criteria for SI diagnosis. Exclusion criteria were as follows: 1) studies with unclear methodologies to obtain the estimates of SI frequency, 2) studies that investigated a statin that has been withdrawn from the market, 3) ongoing trials (unless they reported relevant interim results), 4) studies only investigating statin discontinuation without specifying intolerance, and, 5) short follow-up (<1.5 month/6 weeks).

The search, screening, and data extraction were performed independently by two reviewers (I.B. and J.R.); any disagreements were resolved through discussion with senior investigators (M.B. and P.E.P.). Non-relevant articles were excluded on the basis of title and abstract screening. For each trial, the risk of bias was independently assessed by the same investigators using the revised Cochrane RoB2 tool involving five domains (randomisation process, deviation from intended interventions, missing outcome data, outcome measurement, and selection of reported results). The risk of bias in each study was judged to be “low”, “high” or “unclear” [14]. For the assessment of risk of bias in cohort studies, the Newcastle-Ottawa Scale (NOS) was used. Three domains were evaluated with the following items: a) selection, b) comparability, and, c) exposure. The risk of bias in each study was judged to be “good”, “fair” or “poor” [15].

Outcome measures

The primary endpoint was the overall prevalence, and the prevalence based on each of the international diagnostic criteria: NLA, EAS and ILEP. The secondary endpoint was the prevalence of SI in groups of patients with different diseases and the analysis of the association between possible risk factors/conditions and the risk of SI. According to the NLA, SI is defined as adverse effects relating to quality of life, leading to decisions to decrease or stop the use of an otherwise beneficial drug [8]. The ILEP definition stated that SI is an inability to tolerate a dose of statin required to reduce a person's CV risk sufficiently from their baseline risk and could result from different statin-related side effects [7]. The EAS definition focused only on SAMS: the assessment of the probability of SAMS being due to a statin considering the nature of the muscle symptoms, the elevation in CK levels and their temporal association with statin initiation, discontinuation, and re-challenge [16]. As stated by the CCWG and LLCA, SI was defined as a clinical syndrome characterized by significant symptoms and biomarker abnormalities that is documented by challenge/dechallenge/re-challenge using ≥2 statins that is not due to drug interactions or untreated risk factors for intolerance [9, 10, **Figure S1**]. Because the main outcome was not limited by the type of statin, the CCWG and LLCA criteria were not used in further analyses.

Data synthesis and statistical analyses

The meta-analysis was conducted using R Statistical Software (v3.5.1, Boston, MA, USA), using the packages 'meta' and 'metafor' for meta-analysis. A random-effects model (DerSimonian and Laird method) was applied to estimate the pooled prevalence across the studies. The 95% confidence intervals (CIs) for the prevalence reported in the individual studies (**Table S1**) were estimated from the proportion of cases of SI and sample size using the binomial exact method

(Clopper-Pearson method). An inverse variance method was used for weighting each study in the meta-analysis. For the difference of subgroup analysis, we employed post-hoc analysis. To investigate the differences between groups we used the significance test. An I^2 statistic was also computed for subgroup differences [14]. With the inverse variance method, when the estimated probability of the condition of a single study approaches 0 or 1, the variance of the study approaches zero, which in turn causes the inverse variance to approach infinity; subsequently, the inflated inverse variance substantially increases the adjusted weight of the study in the pooled mean, resulting in an over-contribution of the study in the final pooled estimation of the meta-analysis. Therefore, to avoid the overestimated results, we conducted the Freeman-Tukey double arcsine. The final pooled result and 95% CIs were then back-transformed and expressed as percentages for ease of interpretation. The baseline characteristics are reported as median and range. Mean and standard deviation values were estimated using the method described by Hozo et al. [16]. Heterogeneity between studies was assessed using Cochrane's Q test and the I^2 index. As a guide, I^2 <25% indicated low, 25-50% moderate and >50% high heterogeneity [17].

Potential demographic, clinical and drugs as modifiers of SI were further explored by meta-regression. Meta-regression coefficients and corresponding p-values are reported. For summary estimates, a $p<0.05$ (two-tailed) was considered statistically significant [18].

RESULTS

Study selection and patient population

A total of 3569 articles were retrieved from the search after duplicates from the different databases were discarded. These articles were first screened by title and abstract, leading to 271 articles that underwent full-text review. After a stringent selection process, a total of 176 studies with 4,143,517 patients and a mean follow-up 19±7.3 months were included in the analysis [19-194]. Out of 176 articles, 112 were RCTs (195,575 patients), and the remaining 64 were cohort studies with 3,947,942 patients. The PRISMA flow diagram is shown in **Figure 1,** and the key characteristics of the included studies are presented in **Table S3**. The mean age of patients was 60.5±8.9, and 40.9% were females. The White or Caucasian race made up a greater proportion of participants than Afro-American, Asian, Hispanic or others (81.1%, 8.2%, 5.1%, 4.5% and 1.2%, respectively; $p<0.001$; **Table 1**).

Prevalence of SI

The pooled prevalence of SI was 9.1% (95% CI 8.0-10%, **Figure S2**). The prevalence based on NLA criteria was similar compared with using the ILEP or EAS definitions [7.0 (6.0-8.0%) I^2=98%, 6.7 (5.0-8.0%), I^2=98%, 5.9% (4.0-7.0%), I^2=93%, respectively; **Figure S3, S4, S5**). The prevalence of SI in RCTs was significantly lower compared with cohort studies [4.9 (4.0-6.0%) I^2=93% *vs* 17% (14-19%), I^2=98%; $p<0.001$, **Figure S6 & S7**).

In an analysis stratified by the type of disease prevention, SI was more common in pooled analyses of studies which included both primary and secondary prevention [18% (14-21%, I^2=99%] patients than in either pooled analyses of studies which only included primary or secondary prevention patients [8.2 (6.0-10%, I^2=98%), 9.1% (6.0-11%; I^2=98%), respectively; **Figures 2–4**].

In the subgroup analysis according to disease states, in primary prevention patients with familial hypercholesterolemia (FH), hypercholesterolemia, dyslipidemia, and type 2 diabetes mellitus (T2DM), the prevalence of SI was 9.0% (6.0-13%, I^2=96%), 12% (11-13%, I^2=99%) 13%

(7.0-18%, I^2=98%) and 6.0% (2.0-10%, I^2=99%) (**Figure S8**); respectively. In secondary prevention: stable coronary artery disease (CAD), acute coronary syndrome (ACS), myocardial infarction (MI) and stroke/transient ischaemic attack were associated with SI prevalence of 8% (2.0-18%, I^2=98%) 13 (2.0-24%, I^2=98%), 13 (2.0-24%, I^2=98%) and 5.4% (3.9-9.1%, I^2=96%), respectively (**Figure S9**).

We also compared the prevalence of SI in patients treated with lipophilic (atorvastatin, simvastatin, lovastatin, fluvastatin, and pitavastatin) and hydrophilic statins (pravastatin and rosuvastatin). The pooled prevalence was similar in these two types [4.0 (2.0-5.0%; I^2=97%) *vs* 5.0% (4.0-6.0%, I^2=98%), respectively; p=0.33, **Figure S10 and S11**]. A summary of SI prevalence is shown in **Figure 5**. Between-study heterogeneity was large ($I^2 \geq 93\%$). Tests assessing bias were nonsignificant (p >0.28).

Interaction of demographic indices with SI

In meta-regression analyses, age (as a continuous variable) was found to be significantly associated with the higher risk for SI (OR 1.33, 95% CI 1.25-1.41; p=0.04, **Figure S12A**). Likewise, the older age ≥65 years (OR 1.31, 95% CI 1.22-1.45; p=0.04, **Figure S12B**), and female sex were associated with higher risk of SI (OR 1.47, 95% CI 1.38-1.53; p=0.007) (**Figure S12C**). Analysis of demographic indices revealed that the prevalence of SI was associated with the percentage of participants of Asian and African American race (p<0.05 for both **Figure S12 G and H**). However, no association was observed with White, Caucasian and Hispanic races with SI (p>0.05 for all, **Figure S12 D, E and F**). A summary of the meta-regression of demographic indices on SI is shown in **Figure 6a.**

Interaction of clinical indices with SI

A range of potential factors were tested for possible interaction with SI. Positive associations were found for obesity (OR 1.30, p=0.02), diabetes mellitus (OR 1.26, p=0.02), hypothyroidism (OR 1.37, p=0.01), chronic liver disease (OR 1.24, p=0.03), and chronic renal failure (OR 1.25, p=0.03), whereas the percentage of individuals with depression was found to have a negative association with SI (OR 0.88, p=0.04). Conversely, arterial hypertension was not associated with the prevalence of SI (**Figure S13**).

Interaction of drugs and addiction diseases with SI

The percentage of smokers was not significantly associated with the prevalence of SI (OR 1.03, p=0.60), whereas the percentage of alcohol users used showed a significant association with the prevalence of SI (OR 1.22, p=0.03). Moreover, exercise (OR 1.23, p=0.03), calcium channel blockers (CCB) (OR 1.31, p=0.03) and antiarrhythmic agents (OR=1.35 p=0.03) were associated with higher risk of SI, whereas warfarin use was not (OR 1.04, p=0.15). In addition, increased statin dose was associated with a higher prevalence of SI (OR 1.37, p=0.01), whereas the duration of study follow-up was not associated with the occurrence of SI (OR 1.06, p=0.48, **Figure S14**). A summary of the results of meta-regression with respect to associations between risk factors and drugs on SI is shown in **Figure 6b.**

Risk of bias assessment

The assessment of risk of bias in the included studies using RoB2 for RCTs and NOS for cohort studies showed that most studies had moderate to high quality level in defining objectives and the main outcomes (**Tables S4, S5**).

DISCUSSION

To the best of our knowledge, the present meta-analysis is the first to evaluate the overall prevalence of SI worldwide, the prevalence based on different diagnostic criteria and in different disease settings. The results of our meta-analysis of 176 studies with 4,143,517 patients and a mean follow-up 19±7.3 months showed that the worldwide prevalence of SI is 9.1%, irrespective of the definition applied. Older age, female gender, Asian and African American races, obesity, T2DM, alcohol use, hypothyroidism, chronic liver and renal diseases were associated with higher risk of SI, as were increased statin doses and the concomitant administration of antiarrhythmic agents (**Graphical abstract**).

SI and the discontinuation of statin therapy is an ongoing clinical problem worldwide [1-3]. SI is associated with suboptimal lipid-lowering therapy and a high risk of first and recurrent CVD events [176]. Numerous studies, systematic reviews and meta-analyses have demonstrated an association between statin non-adherence and discontinuation, and the risk of CVD and mortality [195, 196].

Although a wide range of values for the prevalence of SI have been reported in the literature (from 2-3% to as high as 50%) [3, 11, 91, 117], our findings show that the pooled overall worldwide prevalence ranges from 8.1-10% (1 in every 10-12 patients). There is debate on the definition of SI. We compared the prevalence of SI according to all major definitions. Despite the fact that the EAS definition of SI is focused solely on SAMS, the pooled prevalence in our analysis did not show significant differences between the EAS, NLA and ILEP definitions.

The prevalence of SI in cohort studies was significantly higher than that reported in RCTs. This is associated with large difficulties of correct SI diagnosis in clinical practice and lack of possibility of using of new 1-of-trial approach or even cross-over design as it was applied e.g. in

PCSK9 inihibtors trials [197-199]. This also suggests that the prevalence of SI is overestimated in real-life data. It is also possible that RCTs underestimate the prevalence by excluding older patients and those with comorbidities such as chronic liver and kidney diseases, and abnormal laboratory values that may increase the risk of SI. Some previous studies have reported substantially lower adherence rates in primary prevention compared with patients with CVD or after MI [61, 87, 100, 200]. In contrast, our sub-analysis of the pooled prevalence of SI in primary prevention (93 papers with 1,762,384 participants) and in secondary prevention (54 papers with 1,166,745 participants) did not find a significant difference (8.2 *vs* 9.1%). However, in observational cohort studies which included mixed patients (both primary and secondary prevention), the pooled prevalence of SI was twice as high (18%). This finding suggests that such studies overestimate the prevalence of SI. Similarly, in the subgroup analysis based on different diseases in the primary prevention cohorts (FH, hypercholesterolemia, dyslipidemia and T2DM) and secondary prevention (stable CAD, ACS, and MI) the mean overall SI prevalence was not significantly different. Likewise, regarding the safety of different classes of statins, we found no difference between lipophilic and hydrophilic statins.

Because statins are the gold standard for the treatment of dyslipidemia and in the management of elevated CV risk, the most important issue during the diagnosis and management of patients with SI is the urgent need to continue statin therapy. To predict the risk of SI and to be effective in lipid management, it is critically important to know the risk factors and conditions that might increase the risk of SI [4]. It is now 20 years since the ACC/AHA/National Heart Lung and Blood Institute first identified risk factors in their recommendations for statin safety, however, there has been no attempt to validate their suggested risk factors using data from clinical trials or observational studies [201]. In this meta-analysis, we have attempted to investigate what risk factors/conditions might be linked to SI prevalence using meta-regression. Pooled analysis demonstrated that many demographic, clinical and other risk factors are associated with SI. Older age, female gender, Asian and African American races were associated with a higher incidence of SI, whereas White, Caucasian, and Hispanic race were not associated with higher SI risk. Many commonly observed risk factors and conditions may also be significantly associated with SI occurrence, including obesity, diabetes mellitus, hypothyroidism, chronic liver disease and renal failure. Depression was negatively associated with SAMS, perhaps because of under-reporting in these patients [202-205]. Smoking and anticoagulant drugs were not associated with SI, however, the use of alcohol, exercise, antiarrhythmic agents and calcium channel blockers was positively associated with SI. Finally, as previously reported, higher doses of statins were associated with a greater prevalence of SI [5,7].

Strength and limitations: Our meta-analysis has some limitations. Heterogeneity between studies was present in our analysis (I^2=93-99%; unknown confounding may have led to this), although this was anticipated because of the broad scope of this systematic analysis, and due to very large data we could not test the influence analysis that would resolve the effect size of different weight across the studies. The statistical examination of potential publication bias through Egger and funnel plots are not appropriate because studies with less than 100 patients were excluded from this systematic review.

Our analysis depended upon data reported in published studies. Some potential risk factors for SI were not reported with ideal detail or precision, such as the amount of alcohol consumption, types of exercise and physical activity endurance. In this line, race distribution was not similar with predominatly Caucasian/White race (81.1%). It is also important to emphasize the importance of the nocebo/drucebo effect that was not examined in the included studies and might have distorted the final results to some extent (it might be responsible even for >50% of SAMS) [202,206]. However, besides new effective 1-of-trial approach that does not apply in clinical practice, we do not have suitable tools to exclude this phenomenon [199]. Moreover, in most of the included trials the diagnosis was based on the approved definitions, and the final SI prevalence based on this was <7%, what suggests that the potential effect of the nocebo/drucebo effect seemed to be minimized.

The data obtained do not allow us to draw conclusions in relation to the doses of other drugs used in the included studies that could have interacted with statin therapy. Nor can we draw conclusions relating to the stage or severity of diseases such as those affecting the liver, kidney and thyroid. Finally, our analysis cannot be used to suggest appropriate management techniques (e.g. doses of drugs and/or the severity of the diseases when statins might be used without increasing the risk of SI).

CONCLUSION

Based on the data from >4 million patients, we demonstrated that the overall prevalence of SI is relatively low, especially when SI is objectively determined using the recognized international definitions. These results support the concept that the prevalence of complete SI is often overestimated and highlight the need for a very careful assessment of patients with SI, to decrease the risk of unnecessary statin discontinuation and suboptimal lipid-lowering therapy. Clinicians should use these results to encourage adherence to statin therapy in their patients.

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FIGURE LEGENDS:

Figure 1. The Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) flow-chart of studies included in the meta-analysis.

Incomplete data: Studies that reported only statin discontinuation without specifying the reasons for discontinuation.

Figure 2. Prevalence of statin intolerance in primary prevention studies.

Note: D-L random-effects model was used

Figure 3. Prevalence of statin intolerance in secondary prevention studies.

Note: D-L random-effects model was used

Figure 4. Prevalence of statin intolerance in combined primary and secondary prevention studies.

Note: D-L random-effects model was used

Figure 5. Prevalence of statin intolerance – summary figure.

Abbreviations: *NLA – National Lipid Association, ILEP – International Lipid Expert Panel, EAS – European Atherosclerosis Society, RCTs- Randomized Controlled Trials, DM – diabetes mellitus, sCAD – stable coronary artery disease, ASC – acute coronary syndrome, MI – myocardial infarction, TIA – transient ischaemic attack, SI – statin intolerance.*

Figure 6. Summary meta-regression dmographic, risk factors and drugs with SI.

Abbreviations: *SI – statin intolerance, BMI – body mass index, CLD – chronic liver disease, CRF – chronice renal failure, CCB – calcium channel blocker.*

TABLE LEGENDS:

Table 1. Summary of main characteristics of studies included in the present meta-analysis.

Abbreviations: *NLA, National Lipid Association, ILEP, International Lipid Expert Panel, EAS, European Atherosclerosis Society, RCT, Randomized Controlled Trial); Combined: Primary and secondary prevention patients.*

Key question(s)	Key finding(s)	Take-home message
What is the overall prevalence of statin intolerance (SI) worldwide? What are the main risk factors of statin intolerance?	The overall prevalence of SI is 9.1% and even lower using the international definitions; NLA, ILEP, EAS (7.0, 6.7, 5.9%). Female gender, hypothyroidism, high statin dose, advanced age, antiarrhythmics and obesity are the main factors that increase the risk of SI.	Clinicians should use these results to encourage adherence to statin therapy in the patients they treat.