

BMJ Open Statin associated adverse reactions in Latin America: a scoping review

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ABSTRACT

Objectives We aim to describe the frequency and type of adverse drug reactions (ADRs) in patients on statins in published studies from Latin American (LATAM) countries.

Design Scoping review.

Methods A literature search was conducted in three databases (PubMed, EMBASE and LILACS) in addition to a manual search in relevant journals from LATAM universities or medical societies. A snowballing technique was used to identify further references. Randomised controlled trials (RCTs) and observational studies between 2000 and 2020 were included. Studies were considered eligible if they included adults on statin therapy from LATAM and reported data on ADRs. Data on ADRs were abstracted and presented by study design.

Results Out of 8076 articles, a total of 20 studies were included (7 RCTs and 13 observational studies). We identified three head-to-head statin RCTs, two statin-versus-policosanol RCTs and only two placebo-controlled trials. The statin-related ADRs frequency ranged from 0% to 35.1% in RCTs and 0% to 28.4% in observational studies. The most common ADRs were muscle-related events including myalgia and elevated creatine phosphokinase. Other reported ADRs were gastrointestinal symptoms, headache and altered fasting plasma glucose.

Conclusions We identified differences in the frequency of ADRs in both observational studies and RCTs from LATAM countries. This could be due to the absence of standard definitions and reporting of ADRs as well as differences among the study's interventions, population characteristics or design. The variability of ADRs and the absence of definitions are similar to studies from other geographical locations. Further placebo-controlled trials and real-world data registries with universal definitions should follow.

INTRODUCTION

Statin therapy is recommended as an initial treatment for dyslipidaemia and cardiovascular disease (CVD) prevention.^{1–3} However, the role of statins in the primary prevention of CVD has been quite controversial, especially in subjects with low baseline risks.^{4 5} Recently, a meta-analysis of 94 283 patients without a history of CVD found that statins reduced the risk of events such as non-fatal myocardial infarction (absolute risk differences (RD) –20 to –25 to –15 per 10 000 person-years), cardiovascular mortality (RD: –11 to –16 to –5 per 10 000 person-years)

Strengths and limitations of this study

- To our knowledge, this is the first review describing the statin-related adverse reactions in published studies from Latin America.
- A thorough literature search in multiple databases and a manual search was conducted.
- A lack of statin versus placebo randomised controlled trials in the region was identified.
- Most of the randomised controlled trials had small sample sizes and short follow-up periods.
- Some multinational studies including Latin American populations were excluded due to the impossibility of obtaining the segregated data by region.

and major cardiovascular events (RD –14 to –20 to –19 per 10 000 person-years). Concurrently, the aforementioned meta-analysis indicated the need for benefit–harm balance assessments to determine whether statins provide a net benefit.⁶ On the other hand, Koskinas *et al* conducted a meta-analysis of 152 507 patients with a known history of atherosclerotic CVD, among whom statin therapy significantly reduced major vascular events (cardiovascular death, myocardial infarction, coronary revascularisation and stroke) compared with those who were not administered statin therapy (RR: 0.77, 95% CI 0.71 to 0.83).⁷

Notably, despite its benefits, adherence to statin treatment is lower than expected even among patients with a previous cardiovascular event or at high cardiovascular risk.⁸ A systematic review of 19 studies evaluating the predictors of statin adherence in the primary prevention setting found that 17.8%–79.2% of the patients were considered adherent to the therapy.⁹ Furthermore, Kim *et al* conducted an observational study in Korea that included 3807 patients with a recent history of acute myocardial infarction and reported that discontinuing statin therapy was associated with increased mortality.¹⁰ Multiple reasons for statin non-adherence have been cited, including treatment-related

factors such as a high dose or developing adverse drug reactions (ADRs).¹¹

ADRs related to statins, also known as ‘statin-associated symptoms (SAS)’, include statin-associated muscle symptoms (SAMS; myalgia, elevated creatine kinase levels and rhabdomyolysis), diabetes mellitus (DM) and elevated liver enzymes.¹² The prevalence of these events varies depending on the study design. The Patient and Provider Assessment of Lipid Management (PALM) registry in the USA evaluated primary care patients and found that 41.8% of the 5316 current statin users reported at least one SAS.¹³ Meanwhile, in a systematic review of randomised controlled trials (RCTs), the percentage of patients with muscle complaints was 12.7% compared with 12.4% from the placebo group.¹⁴

Ischaemic heart disease is the most common cause of death in Latin America (LATAM).¹⁵ Despite a decrease in mortality in some countries in LATAM, the overall trends in this region are unfavourable when compared with those of North America.¹⁶ A cross-sectional study evaluated the prevalence of dyslipidaemia in seven big cities of LATAM, finding a high prevalence ranging from 38.7% to 68.1%.¹⁷ However, the percentage of patients on lipid-lowering therapy was low (8%–45%).¹⁷ There is a noticeable dearth of studies evaluating the use of statins or the prevalence of ADRs in LATAM. Therefore, in this scoping review, our objectives were to evaluate the frequency of the ADRs related to statin use and describe the different types of ADRs encountered in studies from LATAM.

METHODS

General considerations

A scoping review was conducted following the Arksey and O’Malley framework¹⁸ that was later enhanced by Levac *et al.*¹⁹ We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA) in conducting the review.²⁰ We opted to use a scoping review approach to provide a general overview of the available data on statin-related ADRs, including RCTs and observational studies. Furthermore, we did not anticipate finding many placebo-controlled RCTs for a meta-analysis. Regarding terminology, we used the term ADRs, defined as ‘an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product’²¹ throughout the review.

Objectives and research question

Our objectives were (1) to describe the frequency/prevalence of ADRs and (2) to characterise the different types of ADRs experienced by patients undergoing statin therapy in studies from LATAM countries. We defined our research question using the Population, Intervention, Comparison and Outcome strategy.²² This resulted in the following, P: Adults from LATAM; I: Statin therapy (monotherapy or in combination); C: Any (None, Placebo, Other Statin, Other lipid-modifying therapy

(LMT)) and O: ADRs related to statin therapy, statin intolerance, statin withdrawal.

Eligibility criteria

We included observational (cross-sectional, cohort and case–control studies) and experimental studies (RCTs) that studied adult patients (older than 18 years) undergoing treatment with statins (monotherapy or in combination) from LATAM countries. The studies had to incorporate data on ADRs. The articles included were published between 2000 and 2020. We excluded review articles, case reports or series, and citations in a language that was not Spanish, English or Portuguese given the population of interest (LATAM countries). Notably, during the screening, we did not have to exclude any article based on its language.

Information sources and search strategy

We conducted systematic literature searches through PubMed, EMBASE and LILACS for articles published from inception to August 2020. We used keywords related to statins, ADRs and common statin-related ADRs (muscular, gastrointestinal). The last search was performed on 4 September 2020. The search strategy applied in two of the databases (PubMed and EMBASE) can be accessed in online supplemental material. Additionally, we manually searched university journals from LATAM as well as cardiology, endocrinology and lipid society journals of LATAM countries to find unindexed articles, conference abstracts, or grey literature related to the topic. Lastly, a snowballing technique was employed to identify potential references for the review.

Study selection

Two independent reviewers (MU-J and TP-P) screened the articles by title and abstract using the web application Rayyan.²³ The resulting references were accessed in full text and two authors (MU-J and TP-P) separately selected the articles based on the eligibility criteria. Disagreements were resolved by a third author (CP-C).

Data items and data charting

We developed two independent extraction forms for observational studies and RCTs. Both forms included the general data of the publication (author, year of publication, country, study design, publication type, main objective, funding/conflicts of interest) and the characteristics of the participants (total population, LATAM country/countries, mean age, gender, race, comorbidities, other drugs). Additionally, data regarding statins (whether the participants were on a statin or not, type of statin, dose if available) and outcomes (general outcomes, ADRs, ‘statin intolerance’ with definition if available) were collected. The data extraction form for the RCTs varied by including data about the intervention and comparison of each trial. Whenever we encountered multinational studies without division by region or country, we contacted the corresponding author via email to solicit the needed information. If the reply was negative or no

answer was received, the study was excluded. Moreover, we included multinational trials in which >80% of the study population were from LATAM countries to boost our results.

Synthesis of results

We considered that a narrative synthesis was the best approach for presenting our results given the heterogeneity of the studies. The synthesis was presented according to the study design: RCTs and observational studies. Data on the studies' characteristics, population characteristics, statins, and ADRs are reported.

Patient and public involvement

No patient or public was involved in the design, conduction, reporting, or dissemination of this research.

RESULTS

Study selection

A total of 8076 articles resulted from the initial search. After duplicates were removed, 7862 records were screened by title and abstract, resulting in 180 articles accessed in full text. Finally, 20 articles fulfilled the prespecified inclusion criteria. A PRISMA²⁴ flow chart summarising our selection is shown in figure 1. From the included articles, 7 were RCTs and 13 were observational studies (8 cross-sectional and 5 cohort (2 retrospective and 3 prospective)) studies).

Randomised controlled trials

The studies were from four different LATAM countries (Brazil, Cuba, Mexico and Venezuela)^{25–29} in addition to two multinational studies.^{30,31} From the latter, one included

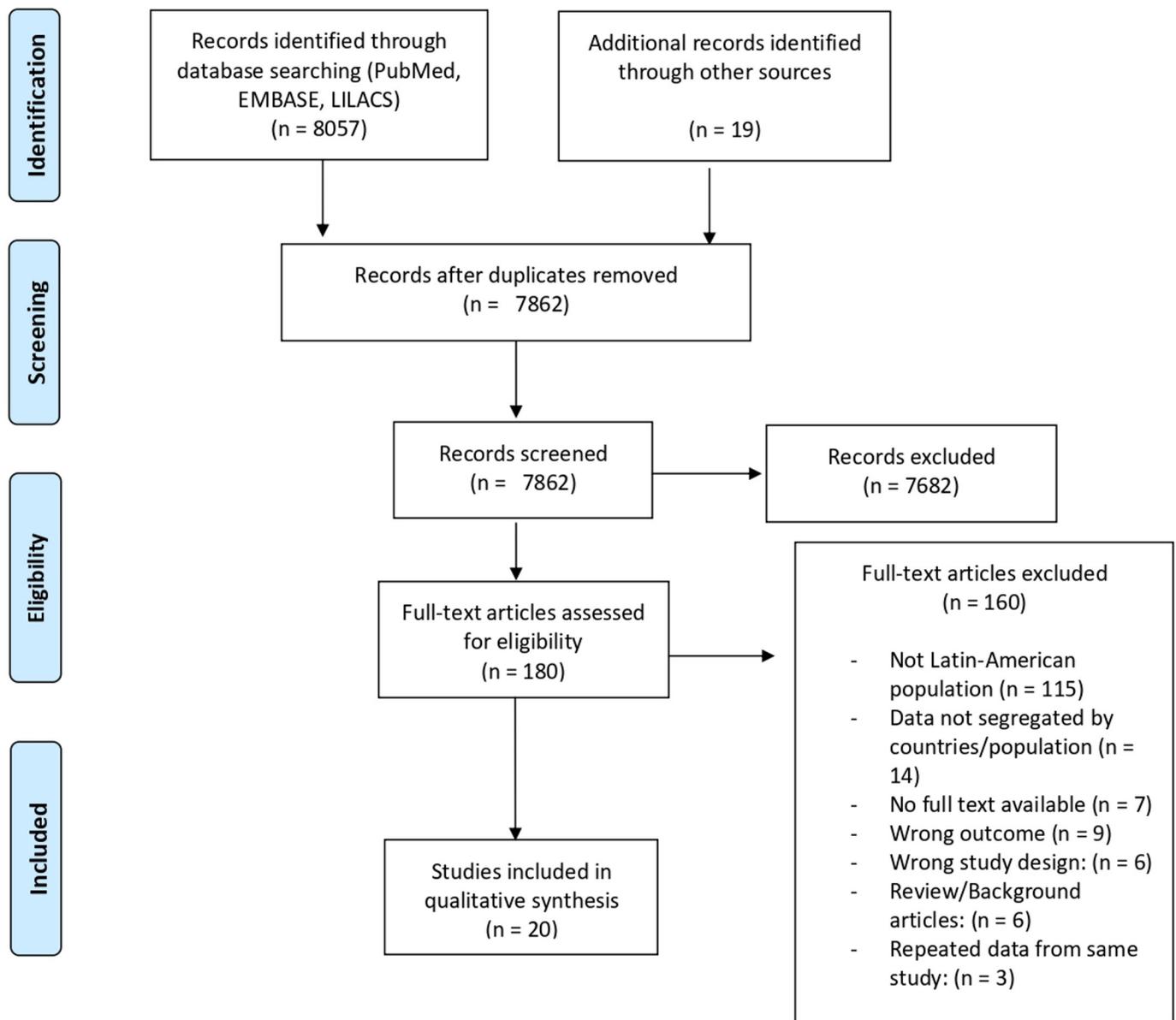


Figure 1 PRISMA²⁴ flow chart for selection of studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

participants from Brazil, Colombia, Mexico and Venezuela (87% of the study population).³⁰ The other divided the outcomes by self-reported ethnicity and the Hispanic group included 88.8% of patients from South and Central America (Argentina, Brazil, Chile, Colombia, Costa Rica, El Salvador, Mexico, Panama, Uruguay and Venezuela).³¹ Four of the RCTs were industry funded,^{25 28 30 31} while the funding source was not disclosed in three.^{26 27 29}

A total of 4209 patients were included across the RCTs. The mean age of the participants ranged from 50 to 66 years.^{25–30} One author reported a median age of 67 years.³¹ The proportion of male participants ranged from 16.3% to 53.2% while female participation ranged from 46.8% to 83.7%, except for one study that included only women.²⁷ The reported baseline characteristics and comorbidities included in the RCTs varied in each report. Mean body mass index (BMI) ranged from 25.7 to 29.1 kg/m².^{26 27 29–31} The most common comorbidities reported were hypertension (HTN) (30.6%–78%),^{25–31} DM (9.4%–54%),^{25–30} obesity (28.6%–41.9%)^{25–27 30} and smoking (10.4%–30.5%).^{25–27 30 31}

Regarding the intervention and comparison, three RCTs were direct statin comparisons^{25 29 30} with one of them being statin/ezetimibe comparison,²⁵ two were statin versus policosanol,^{26 27} and two were placebo-controlled.^{28 31} These studies evaluated both the efficacy and safety of the interventions. The primary outcome or endpoint was mainly the efficacy of treatment; this was evaluated mostly by changes in the low-density lipoprotein cholesterol (LDL-C),^{25–30} the achievement of pre-established LDL-C goals,^{25 29 30} or the reduction of cardiovascular events.³¹ For ADRs evaluation, both clinical and laboratory ADRs were frequently included. Most articles did not include a clear definition of ADRs. [Table 1](#) summarises the characteristics of the RCTs.

Statin ADRs among head-to-head statin (or combination) RCTs

In Brazil, Vattimo *et al* conducted a trial comparing rosuvastatin/ezetimibe versus simvastatin/ezetimibe with a previous simvastatin run-in.²⁵ The frequency of ADRs in the rosuvastatin/ezetimibe arm was 12% during the run-in phase and 19.5% while on the intervention. On the other hand, the simvastatin/ezetimibe arm presented ADRs in 15.8% of the participants during the run-in phase and in 23.8% during the treatment phase.²⁵ The most common ADRs were increased fasting plasma glucose and myalgia.²⁵ Rodríguez-Roa *et al* compared two different presentations of atorvastatin (amorphous highly soluble and crystalline) in Venezuela.²⁹ They segregated the ADRs by type of atorvastatin and reported a frequency of 12.5% and 35.1% among the amorphous highly soluble and crystalline atorvastatin participants, respectively.²⁹ This resulted in an overall prevalence of 24.6%. The most common ADRs were creatine phosphokinase (CPK) elevation (11.5%), abdominal colic (2.9%) and dizziness (2.9%) while 2.9% discontinued treatment.²⁹ Furthermore, Fonseca *et al* (DISCOVERY PENTA study)

compared rosuvastatin to atorvastatin in a multinational study.³⁰ They reported treatment-related ADRs in 25.7% and 21.2%, respectively; serious ADRs in 1.2% and 2.0%, respectively; and discontinuation of treatment in 4.8% and 1.8%, respectively.³⁰ The most common ADRs were headache (1.8% and 1.6%, respectively), myalgia (1.2% and 1.4%, respectively) and dizziness (1.2% and 0.4%, respectively).³⁰

Statin ADRs among statin versus other LMT RCTs

Both trials from Cuba compared 10 mg policosanol to a statin. Castaño *et al* compared policosanol to lovastatin and found ADRs in 6.9% and 30% of the subjects, respectively.²⁶ From the lovastatin arm, 6.7% discontinued treatment; the most common ADRs were gastrointestinal manifestations.²⁶ Meanwhile, Fernández *et al* compared policosanol and fluvastatin,²⁷ and reported that 8.6% and 20% of the patients in the policosanol and fluvastatin groups, respectively, experienced ADRs.²⁷ From the fluvastatin arm, three patients discontinued the study due to ADRs; the most common ADRs were nausea (5.7%) and abdominal discomfort (5.7%).²⁷

Statin ADRs among placebo-controlled RCTs

Talavera *et al* compared the efficacy of rosuvastatin to placebo in reducing triglyceride levels in Mexican patients and reported 'no serious adverse events related to treatment.'²⁸ The Hispanic population of the JUPITER study comparing rosuvastatin versus placebo presented serious ADRs in 8.2% of the participants in the rosuvastatin group compared with 7.9% in the placebo group.³¹ The event rate for serious ADRs per 100 person-years during the follow-up period was 4.75 and 4.55 for rosuvastatin and placebo, respectively.³¹ The number of participants in each group was obtained from the main article of the JUPITER trial.³²

Overall statin ADRs among RCTs

[Table 2](#) presents the prevalence of ADRs in each trial divided by each comparison. Overall, the prevalence of ADRs in the seven included RCTs ranged from 0% to 35.1%.

Observational studies

The studies included were from Argentina (n=3),^{33–35} Brazil (n=4),^{36–39} Colombia (n=4),^{40–43} and Mexico (n=2).^{44 45} A total population of 4680 subjects were evaluated across the studies. The mean age of the participants ranged from 52.5 to 66.4 years.^{33 37–41 43 44} Two authors reported median ages of 45³⁵ and 56 years.⁴² One of the studies evaluated the polypharmacy exclusively in elderly patients (mean age: 72).⁴⁵ Female gender ranged from 11.3% to 77.8%. When reported, BMI ranged from 26.8 to 29.2 kg/m².^{38–41 44} The reported baseline conditions, comorbidities, and lifestyle characteristics varied among the studies. The most common conditions described were HTN (41.2%–88.8%),^{33 36–44} DM (9.9%–63%),^{33 36–41 43 44} coronary heart disease (10.1%–40.6%),^{33 37 41 43 44} smoking (2.8%–65.8%)^{33 36–39 41 43 44}

Table 1 Characteristics of randomised controlled trials (RCTs) included

Reference, year	Country	Main objective	Design	Study population	Population characteristics	Intervention	Comparison	Follow-up time	ADRs definition	ADRs collection	Funding
Vattimo <i>et al.</i> , ²⁵ 2020	Brazil	'To evaluate the efficacy of rosuvastatin/ezetimibe in a noninferiority comparison with simvastatin/ezetimibe for the reduction of LDL-C levels.'	Multicentre, randomised, parallel, open label.	129 subjects	Mean age: 59.28 (SD:±9.1), Female: 63.7%, Primary HC: 63.6%, Mixed DYS: 36.4%, Controlled HTN: 52.7%, Uncontrolled HTN: 20.2%, DM: 34.1%, CHD: 3.1%, Obesity: 41.9%, CKD: 0.8%, MeaS: 66.7%, Smokers: 11.6%	Rosuvastatin 10–20 mg +ezetimibe 10 mg (n=66)	Simvastatin 20–40 mg +ezetimibe 10 mg (n=63)	14 weeks (5 weeks of simvastatin run-in)	ND	ND	Industry-funded (Aché Laboratorios Farmaceuticos)
Castañón <i>et al.</i> , ²⁶ 2000	Cuba	'To compare the efficacy and tolerability of policosanol 10 mg/day and lovastatin 20 mg/day in patients with type II hypercholesterolaemia.'	Randomised, double blind.	59 subjects	Mean age: 50 (SD:±7), Mean BMI: 29.1, Female: 81.4%, HC type Ila: 57.6%, HC type Ilib: 42.4%, HTN: 78%, Obesity: 39%, Smoking: 30.5%, Coronary events: 22%, DM 15.3%	Policosanol 10 mg (n=29)	Lovastatin 20 mg (n=30)	12 weeks	ND	Data from physical exam, laboratory tests and interview at each study visit	ND
Fernández <i>et al.</i> , ²⁷ 2001	Cuba	'To compare the efficacy and tolerability of policosanol with fluvastatin in older hypercholesterolaemic women.'	Randomised, single blind, parallel group in one centre.	70 subjects	Mean age: 66 (SD:±6), Female: 100%, Mean BMI: 27, Primary Ila HC 87.1%, Mixed (Ilib) HC 12.9%, HTN: 67.1%, Obesity: 28.6%, DM: 25.7%, CHD: 24.3%, Smokers: 17.1%.	Policosanol 10 mg (n=35)	Fluvastatin 20 mg (n=35)	12 weeks (4 weeks of diet, 8 weeks of pharmacological treatment)	Severity: serious (fatal/hospitalisation), moderate(discontinuation), mild. Relationship: unlikely, doubtfully, possibly or probably	Data from physical exam, laboratory tests and interviews	ND
Talavera <i>et al.</i> , ²⁸ 2013	Mexico	'To evaluate the efficacy of rosuvastatin in reducing TG levels.'	Randomised, double dummy, double blind, multicentre	334 subjects	Rosuvastatin 10 mg group: Mean age 52.5 (SD ±12.77), Female 46.8%, T2DM 10.8%, HTN 32.43% Rosuvastatin 20 mg group: Mean age 53.14 (SD ±12), Female 59.82%, T2DM 14.29%, HTN 31.25% Placebo group: Mean age 51.48 (SD ±13.47), Female 48.65%, T2DM 11.71%, HTN 30.63%	Rosuvastatin 10 mg (n=111), Rosuvastatin 20 mg (n=112)	Placebo (n=111)	8 weeks	ND	Laboratory tests (glucose, LFTs, creatinine, urea, urine analysis) and the presence of new or increased muscle pain.	Industry-funded (Astrazeneca)
Rodríguez-Roa <i>et al.</i> , ²⁹ 2008	Venezuela	'To compare the effect of two different atorvastatin formulations in Venezuela (Amorphous highly soluble and Crystalline) on LDL-C.'	Double blind, double dummy parallel.	69 subjects	Amorphous atorvastatin: Mean age: 53.98 (SD ±10.8), Female: 75%, Mean BMI: 25.7, HTN: 50%, DM: 9.4% Crystalline atorvastatin: Mean age: 54.8 (SD ±12), Female: 67.5%, Mean BMI: 27.3, HTN: 46%, DM: 54%	Amorphous highly soluble atorvastatin 10 mg or 20 mg (n=32)	Crystalline atorvastatin 10 mg or 20 mg (n=37)	12 weeks (4 weeks of placebo followed by 8 weeks of treatment)	ND	Physical exam and interview in each visit. Laboratory exams (myoglobin, ALT, CPK, proteinuria) at baseline and at 12 weeks.	ND
Fonseca <i>et al.</i> , ³⁰ 2005 (DISCOVERY PENTA)	Multinational	'To compare the efficacy of rosuvastatin and atorvastatin in achieving LDL-C goals.'	Multicentre, randomised, open label trial	1124 subjects	Mean age 59.1 (SD ±11.2), Female 59.4%, Countries: BRA 34.7%, COL 7.6%, MEX: 30.7%, POR: 13.7%, VEN: 13.3%, Mean BMI: 27.8, Obesity: 38%, CVD: 36.9%, HTN: 52.3%, Smokers: 17.1%, DM 18.6%	Rosuvastatin 10 mg (n=531 for efficacy, n=562 for safety)	Atorvastatin 10 mg (n=544 for efficacy, n=562 for safety)	12 weeks	ND	Incidence and severity of ADRs and changes in laboratory tests (LFT, CPK, creatinine)	Industry-funded (Astrazeneca)
Albert <i>et al.</i> , ³¹ 2011 (JUPITER)	Multinational	'To evaluate the effect of statin treatment in primary prevention of cardiovascular events in different race/ethnic groups.'	Randomised, double blind, multicentre.	2281 subjects self-reported as Hispanic	Median age: 67 (IQR 62–72), Female 57%, Median BMI: 28.4, HTN: 55.1%, Current Smoker: 10.4%, MeaS: 56.7%, Regions: SACA: 88.8%, USA/Canada: 11.1%, Europe: 0.001%	Rosuvastatin 20 mg (n=1121)	Placebo (n=1140)	Median follow-up: 1.9 years	ND	Blinded ADRs report	Industry-funded (Astrazeneca)

ADRs, adverse drug reactions; ALT, alanine aminotransferase; BMI, body mass index; BRA, Brazil; CHD, coronary heart disease; CKD, chronic kidney disease; COL, Colombia; CPK, creatine phosphokinase; CVD, cardiovascular disease; DM, diabetes mellitus; DYS, dyslipidaemia; HC, hypercholesterolaemia; HTN, hypertension; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; MeaS, metabolic syndrome; MEX, Mexico; ND, not described; DISCOVERY PENTA, Direct Statin Comparison of LDL-C Values: an Evaluation of Rosuvastatin Therapy; POR, Portugal; SACA, South America and Central America; T2DM, Type 2 diabetes mellitus; TG, triglycerides; VEN, Venezuela.

**Table 2** Prevalence and type of statin related ADRs classified by RCT comparison

Reference	Statin or comparison	ADRs % (n/total pop.)	Type of ADRs			
			Muscle related*	GI symptoms†	FPG alterations	Headache
Head-to-head statin (or combination) RCTs						
Vattimo <i>et al</i> , ²⁵ 2020‡	Ros/Eze 10–20/10 mg	19.5 (13/66)	9% (3% myalgia, 3% increased CPK, 3% low back pain)	0%	4.5%	1.5%
	Sim/Eze 20–40/10 mg	23.8 (15/63)	9.1% (6.1% myalgia, 1.5% increased CPK, 1.5% low back pain)	0%	4.5%	1.5%
Rodríguez-Roa <i>et al</i> , ²⁹ 2008	Amorphous highly soluble atorvastatin 10–20 mg	12.5 (4/32)	6.3% mild increased CPK	6.3% (3.1%: abdominal colic, 3.1%: mild ALT elevation)	N/A	N/A
	Crystalline atorvastatin 10–20 mg	35.1 (13/37)	16.2% increased CPK and 2.7% increased myoglobin	5.4% divided (2.7% diarrhoea and abdominal colic, 2.7% mild ALT elevation)	N/A	N/A
Fonseca <i>et al</i> (DISCOVERY PENTA) ³⁰ 2005	Rosuvastatin 10 mg	25.7 (144/561)	2.4% (1.2% myalgia, 1.2% back pain)	0.6% ALT >3 times ULN (3/532)	N/A	1.8%
	Atorvastatin 10 mg	21.2 (119/562)	1.8% (1.4% myalgia, 0.4% back pain), 0.2% (1/542) CPK >10 times ULN)	0.2% ALT >3 times ULN (1/541)	N/A	1.6%
Statin versus other LMT RCTs						
Castaño <i>et al</i> , ²⁶ 2000	Policosanol 10 mg	6.9 (2/29)	N/A	3.4%	N/A	N/A
	Lovastatin 20 mg	30 (9/30)	3.3% muscle cramps	20%	N/A	N/A
Fernández <i>et al</i> , ²⁷ 2001	Policosanol 10 mg	8.6 (3/35)	N/A	5.7% (acidity)	N/A	N/A
	Fluvastatin 20 mg	20 (7/35)	N/A	11.4% (5.7% nausea, 5.7% abdominal discomfort)	N/A	N/A
Placebo-controlled RCTs						
Talavera <i>et al</i> , ²⁸ 2013	Rosuvastatin 10 or 20 mg	'No serious ADRs'	N/A	N/A	N/A	N/A
	Placebo	'No serious ADRs'	N/A	N/A	N/A	N/A
Albert <i>et al</i> , (JUPITER) ³¹ 2011	Rosuvastatin 20 mg	8.2 (92/1121) event rate§: 4.75	Myopathy: 0.17%, event rate§: 0.1	ALT >3 times ULN: 0.17%, event rate§: 0.1	Newly diagnosed DM: 2.1%, Event rate§: 1.19	N/A
	Placebo	7.9 (91/1140) event rate§: 4.55	Myopathy: 0%	ALT >3 times ULN: 0.08%, event rate§: 0.05	Newly diagnosed DM: 2.1%, event rate§: 1.16	N/A

*Includes myalgia, increased CPK, myopathy, rhabdomyolysis.

†Includes diarrhoea, nausea, gastritis, full stomach, vomiting, liver function tests alteration.

‡This study included a previous simvastatin run-in for 5 weeks where ADRs were reported in 12% and 15.8% of patients in the rosuvastatin/ezetimibe and simvastatin/ezetimibe, respectively.

§Reported as 'adverse event rates per 100 person-years during follow-up'.

ADRs, adverse drug reactions; ALT, alanine aminotransferase; CPK, creatine phosphokinase; DM, diabetes mellitus; FPG, fasting plasma glucose; GI, gastrointestinal; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LMT, lipid modifying therapy; N/A, not available; DISCOVERY PENTA, Direct Statin COmparison of LDL-C Values: an Evaluation of Rosuvastatin therapY; RCTs, randomised controlled trials; Ros/Eze, rosuvastatin/ezetimibe; Sim/Eze, simvastatin/ezetimibe; ULN, upper limit of normal.

and hypothyroidism (2.4%–25.4%).^{37 38 41–43} In addition, a study evaluated the efficacy and safety of rosuvastatin in HIV-positive patients.³⁵ The funding sources of the

studies were as follows: industry (n=4),^{33 41 42 44} non-industry (n=4),^{36–39} none (n=1)⁴⁵ and not described (n=4).^{34 35 40 43}

The type of statin evaluated varied among the observational studies. Two reports described statins as a group.^{33,44} One study included elderly patients taking pravastatin.⁴⁵ Two additional studies assessed participants on individual statins (atorvastatin³⁹ and rosuvastatin³⁵). The remaining manuscripts evaluated multiple types of statins, such as atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin and fluvastatin, as well as combinations with ezetimibe or fibrate. Table 3 summarises the characteristics and definitions for ADRs (when available) of the observational studies.

Statin ADRs among cross-sectional studies

Eight studies had a cross-sectional design.^{33 34 36 38 41 43–45} Cuneo *et al* studied the Argentine population from a large multinational study.³³ They stated that intolerance to a higher dose of statin was the reason for not prescribing the highest dose available for statin in 16.7% of the cases. The most commonly described symptoms were muscle-related and gastrointestinal.³³ Spalvieri *et al* found an overall ADRs prevalence of 23% in an Argentine population.³⁴ These were specified as liver function tests (LFTs) abnormalities (none >three times the upper limit of normal (ULN)) or muscle-related symptoms/CPK elevation.³⁴ Only one participant suffered a severe ADR (CPK elevation >10 times ULN).³⁴ Furthermore, do Nascimento *et al* evaluated the state of statin use in Brazil and found that simvastatin was the preferred statin (90.3%); notably, 6.5% of the users manifested poor adherence (defined as 'missing at least one dose of a statin in the past 7 days').³⁶ Four participants (10.6% of poorly adherent patients and 0.6% of the total population) reported ADRs as the reason for their non-adherence.³⁶ Ferreira Castro *et al* evaluated patients on simvastatin or atorvastatin and found that 17% presented muscle-related ADRs and 2.5% presented a threefold increase in LFTs.³⁸

Ruiz *et al* assessed the state of dyslipidaemia in Colombia and mentioned atorvastatin, rosuvastatin, lovastatin, and simvastatin as the most used statins.⁴¹ ADRs frequency ranged from 4.0% to 5.2%, and statin intolerance was reported in 2.6%.⁴¹ The most common complaints were myalgia, elevated CPK, elevated alanine aminotransferase and gastritis.⁴¹ Furthermore, Toro Escobar *et al* evaluated CPK alterations in patients on statins in a centre in Colombia and showed that 11.1% presented elevated CPK levels, but only 0.6% developed a threefold increase.⁴³ Additionally, 28.4% of the patients complained of muscle pain, 26% of fatigue, and 15.9% of weakness.⁴³ Bello-Chavolla *et al* studied the Mexican population included in a large multinational study and found that 'lack of tolerability' was the reason for not prescribing the highest dose of statins in 13%, describing muscle pain as the most common complaint.⁴⁴ Carrillo-Alarcon *et al* reported that from 24 elderly patients on pravastatin, 12.5% developed ADRs (nausea and dyspepsia).⁴⁵

Statin ADRs among cohort studies

Five studies had a cohort design.^{35 37 39 40 42} Bottaro *et al* assessed rosuvastatin in an HIV-positive population on antiretroviral therapy and found that 3.8% developed ADRs.³⁵ They developed myalgia or gastrointestinal complaints, while one participant had a prominent CPK elevation (19 000 UI/L).³⁵ Smiderle *et al* studied patients on simvastatin or atorvastatin and found an ADRs frequency of 14.9%; myalgia or abnormalities in CPK and/or LFTs were described.³⁷ Meanwhile, Santos *et al* assessed LDL receptor mutations in familial hypercholesterolaemia subjects on atorvastatin and found that 11.6% and 0% of the participants developed myalgia and rhabdomyolysis, respectively, during a 1-year follow-up.³⁹ Zuluaga-Quintero *et al* found an ADRs prevalence of 1.6% among patients with dyslipidaemia on atorvastatin or lovastatin; gastrointestinal distress was the most common symptom.⁴⁰ Interestingly, Diaztagle *et al* reported no ADRs among patients on rosuvastatin or statin in combination with fibrates or ezetimibe in patients from 12 Colombian cities; however they noted that only 39% of the patients attended their second follow-up.⁴²

Overall statin ADRs among observational studies

Table 4 presents the frequency of ADRs related to statin therapy among the observational studies divided by study design. Overall, the frequency of ADRs among the included observational studies ranged from 0% to 28.4%.

DISCUSSION

This scoping review identified a high variation in the frequency of statin-related ADRs among experimental and observational studies in LATAM countries. Among the RCTs, the percentage of patients with ADRs ranged from 0% to 35.1%, whereas in the observational studies, this proportion ranged from 0% to 28.4%. Most studies did not clearly define the ADRs, while in those that did, the definitions and types of ADRs reported were heterogeneous. The most frequently encountered ADRs were muscle-related manifestations, including CPK elevation, myalgia and myopathy.

The included RCTs differed in crucial aspects such as the type of statin, doses, follow-up time and, most importantly, comparisons. We included three head-to-head, two statin-versus-policosanol, and two placebo-controlled trials. From the latter, Talavera *et al* reported no serious ADRs in either group,²⁸ while Albert *et al* described a similar event rate for developing ADRs in both groups.³¹ A meta-analysis described that many of the commonly reported and serious ADRs occurred at a similar rate in both statins and placebo.⁴⁶ Notably, Penson *et al* introduced the 'drucebo' concept in an attempt to better describe the 'placebo' and 'nocebo' effects due to drugs.⁴⁷ They conducted a systematic review evaluating SAMS in RCTs that included both open-label and blinded phases and described that 38%–78% of the SAMS in RCTs could be due to a 'negative drucebo effect' rather

Table 3 Characteristics of observational studies included

Reference, year	Country	Main objective	Design	Study population	Population characteristics	Statins included	ADRs definition	ADRs collection	Funding
Cuneo <i>et al.</i> , ³³ 2019	Argentina	'To evaluate the percentage of patients in very high and high cardiovascular risk that reach LDL-c goals according to European Society of Cardiology 2011 guidelines.'	Cross-sectional study	307 patients	Mean age 63.7 (SD:±12.1), Female 40.4%, HTN: 72.6%, DM: 11.4% 22.1%, Smokers: 10.4%, Obesity: 31.3% CHD: 31.6%, Cerebrovascular disease: 6.2%, CKD: 7.2%	97.4% on statins (78.2% monotherapy, 11.4% combination with cholesterol absorption inhibitor, 5% combination with fibrates.)	ND	ND, 'most commonly reported intolerance symptoms'	Industry-funded (Sanofi)
Spalvieri <i>et al.</i> , ³⁴ 2011	Argentina	'To establish the incidence of adverse events caused by statins used in patients with dyslipidaemia (mainly myositis).'	Cross-sectional study	623 patients	<45 years: 4.2%, 45–60 years: 33.9%, >60 years: 61.9%, Female: 58.5%	Atorvastatin 51%, Simvastatin 29.1%, Rosuvastatin 13%, Lovastatin 3.7%, Fluvastatin 2.4%, Pravastatin 0.8%	ND	Survey for self-reported ADRs during treatment. CPK and ALT levels.	ND
Bottaro <i>et al.</i> , ³⁵ 2008	Argentina	'To evaluate the efficacy and safety of rosuvastatin in HAAART-treated HIV-infected patients with dyslipidaemia, and moderate to high cardiovascular risk.'	Cohort study	78 patients	HIV infected on HAART. Median age 45 (30–68), Male 89.7%	Rosuvastatin (monotherapy 76.9%, rosuvastatin plus fibrate 23%)	Hepatic toxicity: elevation of LFTs>5 times ULN (previously normal) or >3.5 times ULN (abnormal baseline). Digestive toxicity: GI symptoms leading to statin withdrawal. Muscular toxicity: elevation of CPK>10 times ULN or myalgia/weakness leading to statin withdrawal.	Through health records review	ND
do Nascimento <i>et al.</i> , ³⁶ 2018	Brazil	'To determine and characterise statin use in primary healthcare delivered by the public health system in Brazil.'	Cross-sectional study	603 statin users from 6511 medicine users.	18–44 years: 9.6%, 45–64 years: 60%, >65 years: 30.4%, Female 77.8%, Smokers 14.4%, HTN: 73%, DM: 36.6%, DYS: 81.4%	Simvastatin 90.3%, Atorvastatin 4.7%, Rosuvastatin 1.9%	ND	Self-reported questionnaire on use of medicines	Non-Industry funded (Brazilian Ministry of Health)

Continued

Table 3 Continued

Reference, year	Country	Main objective	Design	Study population	Population characteristics	Statins included	ADRs definition	ADRs collection	Funding
Smiderle <i>et al.</i> , ³⁷ 2014	Brazil	'To determine the effects of sexual dimorphism and interaction with co medications on the efficacy and safety of simvastatin and atorvastatin.'	Cohort study	495 patients	Mean age: 61.5 (SD ±10.9), Female: 66.9%, Current smokers: 8.7%, Prior CVD: 32.5%, DM: 18.7%, HTN: 71.3%, hypothyroidism: 15.1%	Simvastatin 85.1%, Atorvastatin 14.9%	<i>Muscular</i> : Myalgia (muscle pain with or without CPK elevation) concomitant with statin therapy. Liver impairment: elevation of ALT or AST concomitant with statin therapy.	Physical exam, clinical data and laboratory obtained by physician every 3 months.	Non-Industry funded (CNPq)
Ferreira Castro <i>et al.</i> , ³⁸ 2017	Brazil	'To study factors associated with statin related adverse muscular events.'	Cross-sectional study	120 patients	Mean age 60.9 (SD:±11.2), Mean BMI: 29.2, Female: 56%, T2DM: 63%, HTN: 65%, Obesity: 32%, Hypothyroidism 13%, CKD: 5%, Smokers: 27%.	Simvastatin 70%, Atorvastatin 25%, Rosuvastatin 4%, Pravastatin 1%	Muscular: serum CK elevation, any degree of myopathy, myalgia, myositis, or rhabdomyolysis.	Medical records of physical exam, patient's complaints, and laboratory tests. CNP1)	Non-Industry funded (Brazilian Ministry of Education and Education and CNP1)
Santos <i>et al.</i> , ³⁹ 2014	Brazil	'To assess the influence of the presence and type of LDL receptor mutation on lipid profile and the response to lipid-lowering therapy in patients with heterozygous familial hypercholesterolaemia.'	Cohort study	156 patients	Mean age 52.5 (SD ±14.5), Female: 67.9%, Mean BMI female: 27.5, Mean BMI male: 26.7, HTN: 58.3%, DM: 14.7%, Female smokers: 7.6%, Male smokers: 16%	Atorvastatin	Muscular: myalgia (atorvastatin-induced muscle pain irrespective of CK values at onset of treatment or in dose-up titration until the first year of follow-up), CK elevations >3 times ULN (irrespective of symptoms) and rhabdomyolysis.	Patient assessment and CK levels at least three times during follow-up.	Non-Industry Funded (FAPESP)
Zuluaga-Quintero <i>et al.</i> , ⁴⁰ 2015	Colombia	'To describe changes on lipid profile in patients with dyslipidaemia under treatment with statins in a cardiovascular risk programme.'	Cohort study	183 patients	Mean age 56.8 (SD:±11.4), Female 58.3%, Mean BMI pre-treatment: 27.2 and post treatment 26.7, HTN 88.8%, DM: 25.7%.	Atorvastatin and Lovastatin	ND	Patient's health records	ND

Continued

Table 3 Continued

Reference, year	Country	Main objective	Design	Study population	Population characteristics	Statins included	ADRs definition	ADRs collection	Funding
Ruiz <i>et al</i> , ⁴¹ 2020	Colombia	'To describe the frequency of dyslipidaemias.'	Cross-sectional study	461 patients	Mean age 66.4 (SD ±12.3), Female: 53.4%, Mean BMI 26.8, HTN: 63.1%, CVD: 40.6%, DM: 27.5%, Hypothyroidism: 25.4%, CKD: 16.3%, Current smoker: 2.8%	Atorvastatin 75.7%, Rosuvastatin 24.9%, Lovastatin 8.9%, Simvastatin 5.4%	ND	One patient visit and previous health records	Industry-funded (Sanofi)
Diaztagle <i>et al</i> , ⁴² 2019	Colombia	'To describe the clinical performance and safety of the use of lipid-lowering treatment in patients with dyslipidaemia in real medical practice.'	Cohort study	501 patients	Median age 56 (IQR:48–67), Female: 62.3%, HTN: 64.4%, Hypothyroidism: 2.4%	80.3% taking statin as monotherapy or combination: Rosuvastatin 30.5% Atorvastatin/Ezetimibe 20.7% Rosuvastatin/Ezetimibe 15.3% Rosuvastatin/Fenofibrate 13.5%	ND	Interview, physical exam, and self-report through predefined platform	Industry-funded (Abbot–Lafanco)
Toro Escobar <i>et al</i> , ⁴³ 2010	Colombia	'To determine the prevalence of elevated CPK in patients under treatment with statins and to identify possible risk factors associated with increased CPK in these patients.'	Cross-sectional study	503 patients	Mean age 58.9 (SD ±10.9), Female: 51.5%, Smokers: 7.8%, DM: 9.9%, HTN: 41.2%, CHD: 10.1%, hypothyroidism: 19.1%	Lovastatin 38% Atorvastatin 33.8%, Simvastatin 21.3%, Rosuvastatin 5.4%, Other 1.6%	<i>Muscular:</i> Pain: subjective sensation associated or not with exercise/ADLs related with statin use. Fatigue/Tiredness: self-reported associated or not with exercise/ADLs as strength loss.	Survey (clinical data and laboratory tests)	ND
Bello-Chavolla, ⁴⁴ 2019	Mexico	'To investigate factors associated with the achievement of LDL-C goals in Mexico using real-life data.'	Cross-sectional study	626 patients	Mean age 59.3 (SD ±12.7), Median BMI 28.8, Female: 55.6%, HTN: 58%, T2DM: 58%, Obesity: 40%, Smokers 65.8%, CAD: 14.4%	97.4% of patients were receiving statin therapy.	ND	Questionnaire completed by physician that collected data of patient (case report form) and physician	Industry-funded (Sanofi)

Continued

Table 3 Continued

Reference, year	Country	Main objective	Design	Study population	Population characteristics	Statins included	ADRs definition	ADRs collection	Funding
Carrillo-Alarcon, ⁴⁵ 2015	Mexico	'To determine characteristics of polypharmacy in older adults three units in Hidalgo, Mexico.'	Cross-sectional study	24 statin users from 282 medication users.	N/A	Pravastatin	ND	Survey	None

ADLs, activities of daily living; ADRs, adverse drug reactions; ALT, alanine aminotransferase; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CNPq, Brazilian National Council for Scientific and Technological Development; CPK, creatinine phosphokinase; CVD, cardiovascular disease; DM, diabetes mellitus; DYS, Dyslipidaemia; FAPESP, The São Paulo Research Foundation; HAART, highly active antiretroviral therapy; HTN, hypertension; LDL-c, low-density lipoprotein cholesterol; LFTs, liver function tests; ND, not defined; T2DM, type 2 diabetes mellitus; ULN, upper limit of normal;

than to a direct effect of statin treatment.⁴⁷ On the other hand, the placebo effect has been debated.⁴⁸ Factors such as possible average neutrality of effects, patient selection and selective inclusion of certain outcomes may lead to misinterpretation of RCT data on ADRs.⁴⁸

Regarding the observational studies, the lower end of this range was attributed to the findings from Diaztagle *et al*, who considered that this low rate of ADRs can be explained by the nonattendance of the subjects in their second follow-ups after the prescription of therapy.⁴² In contrast to these findings, a cross-sectional study from the PALM registry in the USA found that 41.8% of current statin users and 63.2% of former statin users complained of at least one symptom associated with statin therapy.¹³ Moreover, a multinational clinician web-based survey was conducted in two different studies which described that, according to physicians, the estimated percentage of patients unable to tolerate statins was 6% (2%–12% among 13 countries)⁴⁹ and 2.7% (1.1%–4.8% among 12 countries),⁵⁰ with muscular symptoms being the most common overall.^{49 50}

The differences in the definitions and reporting of ADRs may account for the variations in the frequency in our review. Most of the included RCTs did not define ADRs. This problem was also encountered by Ganga *et al*, who conducted a meta-analysis of muscle-related ADRs and found that 98% of the studies did not provide a definition for them.¹⁴ Other factors have been posited to affect the appearance of ADRs in statin users.⁵¹ Some authors have stated that female gender and advanced age may be risk factors for muscle-related ADRs.^{51 52} From the included articles, two exclusively comprised older populations,^{27 45} while one focused only on female participants.²⁷ In addition, comorbidities such as metabolic syndrome, obesity, and HTN or the use of concomitant drugs may also impact the rate of ADRs.⁵¹ The included studies varied greatly on their baseline characteristics and comorbidities like DM, HTN and obesity. One study included only HIV-positive patients on antiretrovirals.³⁵ The included studies evaluated patients on different statins and doses. A dose-related response has been described previously in some ADRs, such as muscle-related ones⁵³ and rhabdomyolysis.⁵⁴ An additional factor that may affect the estimation of ADRs in published studies is the selection of patients in RCTs, as subjects with an increased risk of developing muscle-related ADRs may have been excluded.⁵⁵ Lastly, the association of funding sources with outcomes on RCTs has been discussed.⁵⁶ Approximately half (3/7) and a third (4/13) of the included RCTs and observational studies, respectively, did not have information available regarding the funding source.

The present review has some limitations that need to be mentioned. First, we had to exclude 14 multinational studies that fulfilled the initial eligibility criteria because the data were not segregated by region, leading to the loss of valuable information for our review. Second, most of the RCTs had small sample sizes and short follow-up periods. Studies with small samples can affect the

**Table 4** Prevalence and type of statin related ADRs classified by study design

Reference	Statins included	ADRs % (n/total pop.)	Type of ADRs			
			Muscle related*	GI symptoms†		
Cross-sectional studies						
Cuneo <i>et al</i> , ³³ ‡ 2019	Any statin in monotherapy or combination with fibrate or cholesterol absorption inhibitor	16.7 (42/255)	26 cases	12 cases		
Spalvieri <i>et al</i> , ³⁴ 2011	Atorvastatin, simvastatin, rosuvastatin, lovastatin, fluvastatin, pravastatin	23 (145/623)	11% (myositis, myalgia, elevated CPK)	12% elevated ALT		
do Nascimento <i>et al</i> , ³⁶ 2018	Simvastatin, atorvastatin, rosuvastatin	0.6 (4/603)	N/A	N/A		
Ferreira Castro <i>et al</i> , ³⁸ 2017	Simvastatin, atorvastatin	20 (24/120)	17.5%	2.5% elevated LFT three times ULN		
Ruiz <i>et al</i> , ⁴¹ 2020	Simvastatin Rosuvastatin Atorvastatin	4.0 4.3 5.2	'Myalgia was the most common, followed by elevated CPK'	ALT elevation and gastritis followed the muscle related.		
Toro Escobar <i>et al</i> , ⁴³ 2010	Lovastatin, atorvastatin, simvastatin, rosuvastatin	28.4 (143/503)			28.4% myalgia, 11.1% elevated CPK	N/A
Bello-Chavolla ⁴⁴ ‡ 2019	Any statin in monotherapy or combination with fibrate or cholesterol absorption inhibitor	13			'Muscle pain was the most common (24%)'	
Carrillo-Alarcon, ⁴⁵ 2015	Pravastatin	12.5 (3/24)	N/A	12.5% (nausea and dyspepsia)		
Cohort studies						
Bottaro <i>et al</i> , ³⁵ 2008	Rosuvastatin	3.8 (3/78)	2.6% myalgia	1.2%		
Smiderle <i>et al</i> , ³⁷ 2014	Simvastatin, atorvastatin	14.9 (74/495)	9.6% myalgia	5.3% elevated CPK and/or abnormal LFT		
Santos <i>et al</i> , ³⁹ 2014	Atorvastatin	11.6 (17/156)	11.6% myalgia	N/A		
Zuluaga-Quintero <i>et al</i> , ⁴⁰ 2015	Atorvastatin, lovastatin	1.6 (3/183)	0%	'GI related ADR were the most common'		
Diaztagle <i>et al</i> , ⁴² 2019	Rosuvastatin, atorvastatin/ ezetimibe, rosuvastatin/ ezetimibe, rosuvastatin/ fenofibrate	0 (0/501)	N/A	N/A		

*Includes myalgia, increased CPK, myopathy, rhabdomyolysis.

†Includes diarrhoea, nausea, gastritis, full stomach, vomiting, liver function tests alteration.

‡These authors describe the reasons for not prescribing the highest dose possible of statins and the percentage that is due to intolerance.

ADRs, adverse drug reactions; ALT, alanine aminotransferase; CPK, creatine phosphokinase; FPG, fasting plasma glucose; GI, gastrointestinal; LFT, liver function test; N/A, not available; ULN, upper limit of normal.

precision of outcomes in RCTs.⁵⁷ In this case, it can lead to overestimation or underestimation of the prevalence of ADRs, especially when percentages are used. RCTs with short follow-up periods may miss data on long-term ADRs.⁵⁸ Third, three out of seven RCTs were head-to-head comparisons of statins resulting in a more of an observational type of result as no alternative or placebo was present for comparison. Fourth, an inherent limitation of any review is relying on the ADRs reported in

manuscripts, and not necessarily all of those reported by patients which could lead to underreporting of ADRs.⁵⁹

To our knowledge, this is the first review to collate and describe the data of statin-related ADRs in the LATAM population. We conducted a thorough systematic search in multiple databases and an important manual search, including studies from various countries from the region and two large multinational studies. This scoping review identified an important gap in the literature regarding

statin ADRs in LATAM. Our work should encourage researchers and/or public health entities in LATAM countries, especially those where no studies were identified, to develop studies or registries that describe the use of statins, including indications for treatment, the most prescribed/used statin, ADR frequency and discontinuation rates. In addition, the use of clear and consistent ADRs definitions in upcoming studies is crucial.

CONCLUSIONS

In this review, we identified differences in the frequency of ADRs among published studies in LATAM. A high variation in ADRs reporting was found to be a reflection of the differences in the definitions and measurements of ADRs among statin studies in the region. The variability of ADRs and the absence of definitions are similar to those noted in studies from other geographic locations. These deficits indicate the need for the standardisation of definitions and measurements for statin ADRs in future studies. Further placebo-controlled trials with extensive eligibility criteria and longer follow-ups, as well as real-world data studies, evaluating statin ADRs in LATAM are warranted.

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Contributors MU-T had the research idea. MU-J, TP-P and MU-T contributed to the conceptualisation of the review. TP-P and CP-C conducted the literature search. MU-J, TP-P and CP-C did the screening of abstracts and full texts. MU-J, TP-P, CP-C and MU-T contributed to the data charting. MU-J, TP-P, CP-C and MU-T interpreted the data. MU-T supervised the review. MU-J wrote the initial manuscript draft. MU-J, TP-P, CP-C and MU-T were involved in the critical revision of the article. All authors read and approved the final draft.

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