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Statin-Associated Allergic and Cutaneous Adverse Reactions: A Systematic Review

Yasmin Sângela de Paula Oliveira[1]; Yure Cauã de Paula Oliveira[2]

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SYSTEMATIC REVIEW

ABSTRACT

Statins (HMG-CoA reductase inhibitors) are among the most widely prescribed drugs globally; however, statin-associated allergic and cutaneous reactions remain underreported and poorly characterised. This study aimed to systematically identify, describe, and quantify the spectrum of such reactions, characterising implicated agents, severity, proposed immunological mechanisms, and clinical outcomes. A systematic review was conducted following PRISMA 2020 guidelines, searching PubMed/MEDLINE, Cochrane Library, and LILACS/BVS (May 2026), by two independent reviewers (κ=0.673; PROSPERO: CRD420261391101). Of 296 records identified, 25 studies were included (22 case reports, 2 case series, 1 observational study; 14 countries). Atorvastatin was the most frequently implicated agent (n=10; 40.0%), followed by rosuvastatin (n=5; 20.0%) and simvastatin (n=4; 16.0%). Angioedema was the most common reaction (n=6; 24.0%), followed by drug eruptions (20.0%) and autoimmune/systemic reactions (16.0%). Severe reactions accounted for 40.0% of cases. Complete resolution after drug discontinuation was documented in 88.0%, with an overall resolution rate of 96.0%. Statins can induce a broad and clinically significant spectrum of allergic and cutaneous reactions; prompt drug withdrawal is the cornerstone of management.

Keywords: Hydroxymethylglutaryl-CoA Reductase Inhibitors. Drug Hypersensitivity. Urticaria. Angioedema. Drug Eruptions.

Reações Alérgicas e Cutâneas Associadas ao Uso de Estatinas: Uma Revisão Sistemática

RESUMO

As estatinas (inibidores da HMG-CoA redutase) figuram entre os medicamentos mais prescritos globalmente, porém as reações alérgicas e cutâneas associadas ao seu uso permanecem subnotificadas e mal caracterizadas. O objetivo deste estudo foi identificar, descrever e quantificar o espectro dessas reações, caracterizando os agentes implicados, a gravidade, os mecanismos imunológicos propostos e os desfechos clínicos. Foi conduzida uma revisão sistemática seguindo as diretrizes PRISMA 2020, com buscas nas bases PubMed/MEDLINE, Cochrane Library e LILACS/BVS (maio/2026), por dois revisores independentes (κ=0,673; PROSPERO: CRD420261391101). Dos 296 registros identificados, 25 estudos foram incluídos (22 relatos de caso, 2 séries de casos, 1 estudo observacional; 14 países). A atorvastatina foi o agente mais implicado (n=10; 40,0%), seguida de rosuvastatina (n=5; 20,0%) e sinvastatina (n=4; 16,0%). O angioedema foi a reação mais frequente (n=6; 24,0%), seguido de erupções medicamentosas (20,0%) e reações autoimunes/sistêmicas (16,0%). Reações graves representaram 40,0% dos casos. Resolução completa após suspensão do fármaco foi documentada em 88,0% dos casos, com taxa global de resolução de 96,0%. Conclui-se que as estatinas podem induzir um espectro amplo e clinicamente significativo de reações alérgicas e cutâneas; a suspensão imediata do medicamento constitui o pilar do manejo clínico.

Palavras-chave: Inibidores de HMG-CoA Redutases. Hipersensibilidade a Drogas. Urticária. Angioedema. Erupções por Drogas.

[1] Medicine Course, Universidade do Estado do Rio Grande do Norte (UERN), Mossoró, RN, Brazil
[2] Medicine Course, Universidade Federal Rural do Semi-Árido (UFERSA), Mossoró, RN, Brazil

Autor correspondente: Yasmin Sângela de Paula Oliveira – yasminsangela@hotmail.com

INTRODUCTION

Statins, or HMG-CoA reductase inhibitors, constitute one of the most prescribed drug classes globally, with hundreds of millions of patients receiving long-term therapy for hypercholesterolaemia and cardiovascular risk reduction.[1] Available agents include atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, and pitavastatin, all sharing a mechanism of competitive inhibition of the rate-limiting enzyme in cholesterol biosynthesis.

The safety profile of statins has been extensively studied. Well-recognised adverse effects include myopathy, rhabdomyolysis, elevated transaminases, and new-onset diabetes mellitus.[2] Meta-analyses have quantified the incidence of these reactions across large randomised controlled trial populations.[3] However, allergic and cutaneous adverse reactions — including pruritus, urticaria, angioedema, lichenoid eruptions, fixed drug eruptions, photosensitive reactions, and severe systemic hypersensitivity syndromes such as drug reaction with eosinophilia and systemic symptoms (DRESS) — have received comparatively little systematic attention.

These reactions are predominantly reported as isolated case reports and small case series, limiting clinicians' ability to anticipate, recognise, and manage them appropriately. Existing reviews have focused primarily on musculoskeletal and hepatic outcomes,[3] leaving a clear gap regarding the spectrum, frequency, and management of statin-associated hypersensitivity and cutaneous reactions. Failure to recognise a statin as the causative agent may lead to inappropriate continuation of therapy, use of cross-reactive agents, or delayed treatment.

To address this gap, we conducted a systematic review of studies reporting allergic and cutaneous adverse reactions associated with any statin, aiming to characterise their clinical presentation, implicated agents, proposed immunological mechanisms, and outcomes following drug discontinuation.

METHODOLOGY

Protocol and Registration

This systematic review was conducted following PRISMA 2020 guidelines.[4] The protocol was prospectively registered in PROSPERO (CRD420261391101).

Eligibility Criteria

Studies were eligible if they fulfilled PICo criteria: (1) Population — human patients of any age receiving any statin at any dose; (2) Interest — development of at least one allergic or cutaneous adverse reaction, including pruritus, urticaria, angioedema, maculopapular eruption, lichenoid drug eruption, fixed drug eruption, photosensitive reaction, DRESS syndrome, lupus-like reaction, dermatomyositis-like syndrome, erythema multiforme, or anaphylaxis; (3) Context — any clinical setting and geographic region. Studies published in English, Portuguese, or Spanish were included with no date restriction.

Studies were excluded if they: (1) involved only animal or in vitro models; (2) did not describe a specific allergic or cutaneous reaction; (3) were editorials, opinion pieces, or narrative reviews without original primary clinical data; (4) were conference abstracts; or (5) reported duplicate cases.

Information Sources and Search Strategy

Searches were performed in PubMed/MEDLINE, Cochrane Library, and LILACS/BVS in May 2026 using MeSH terms and free-text keywords with Boolean operators. Complete search strings are provided in Supplementary Appendix 1.

Study Selection, Data Extraction and Quality Assessment

Records were imported into Rayyan (https://www.rayyan.ai) for duplicate removal and screening by two independent reviewers, blinded to each other's decisions. Discordant decisions were resolved by consensus. Inter-rater agreement was assessed using Cohen's kappa (κ=0.673; substantial agreement). Data were extracted using a standardised a priori form covering: bibliographic data; study design; statin type and dose; reaction type and severity; time to onset; management; resolution; rechallenge; causality (Naranjo scale); mechanism; and demographics. Methodological quality was assessed with JBI Critical Appraisal Checklists. A narrative synthesis was conducted given the heterogeneity of included studies.

RESULTS AND DISCUSSION

Study Selection

Database searches yielded 296 records (PubMed: 24; Cochrane Library: 257; LILACS/BVS: 15). After removal of 75 duplicates, 221 records were screened, resulting in 182 exclusions. Thirty-nine articles were assessed by full-text review; 14 were excluded (Supplementary Appendix 2), yielding 25 included studies. The selection process is illustrated in Figure 1.

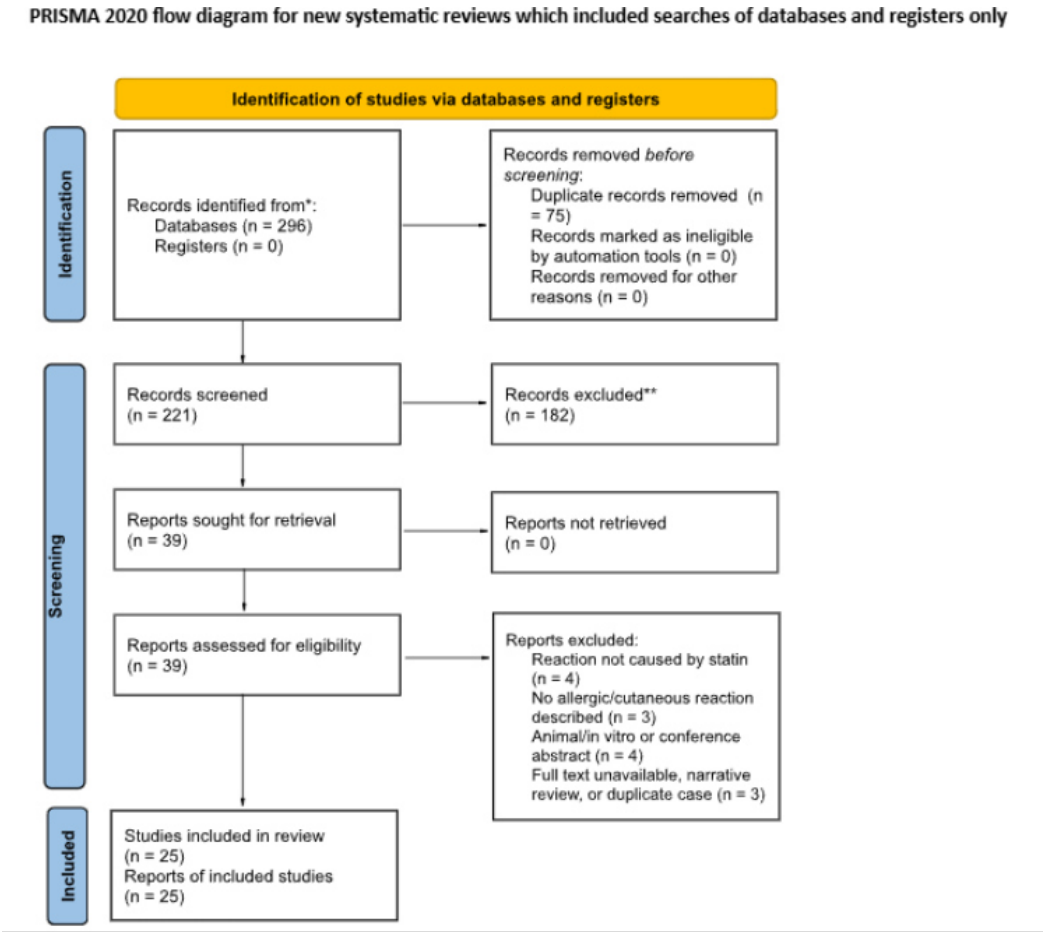

Figure 1. PRISMA 2020 flow diagram of study selection.
Source: Adapted from Page et al. (2021).

Characteristics of Included Studies

The 25 included studies were published between 1994 and 2023, from 14 countries across five continents (USA: 11; UK: 2; Spain: 2; others: 1 each). Study designs comprised 22 case reports (88.0%), 2 case series (8.0%), and 1 observational study (4.0%). Atorvastatin was the most frequently implicated agent (n=10; 40.0%), followed by rosuvastatin (n=5; 20.0%), simvastatin (n=4; 16.0%), pitavastatin (n=1; 4.0%), and pravastatin (n=1; 4.0%); two studies involved multiple or unspecified statins (8.0%). Characteristics are presented in Table 1.

Table 1. Characteristics of included studies.

Author (Year)	Country	Design	Statin	Reaction	Severity	Time to onset	Resolution	Rechallenge	Causality
Pua VS et al.	Australia	CR	Pravastatin	Lichenoid eruption	Moderate	Weeks	Yes	NR	Probable
Roger D et al.	France	CR	Simvastatin	Lichenoid eruption	Moderate	Weeks	Yes	NR	Probable
Zgolli F et al.	Tunisia	CR	NR	Angioedema (recurrent)	Severe	NR	Yes	Yes	Definite
Hanson K et al.	USA	CR	Atorvastatin	Drug eruption	Moderate	Weeks	Yes	NR	Probable
Pop M et al.	USA	CR	Atorvastatin	Acute hypersensitivity	Severe	<24h (1st dose)	Yes	NR	Definite
Oda T et al.	Japan	CR	Rosuvastatin	Drug eruption	Moderate	Weeks	Yes	NR	Probable
Trcko K et al.	Slovenia	CR	Atorvastatin	Lupus erythematosus tumidus	Moderate	Weeks-months	Yes	NR	Probable
Naz S et al.	Pakistan	CR	Pitavastatin	Angioedema	Severe	NR	Yes	NR	Probable
Voloshyna D et al.	USA	CR	Atorvastatin	Angioedema	Severe	NR	Yes	NR	Probable
Shahbaz A et al.	USA	CR	Rosuvastatin	Angioedema	Severe	NR	Yes	NR	Probable
Mustafa SF et al.	USA	CR	Rosuvastatin	DRESS syndrome	Severe	2-8 weeks	Yes	NR	Probable
Malik S et al.	USA	CR+Rev	Rosuvastatin	Pruritus	Mild-moderate	Days-weeks	Yes	NR	Probable
Khan S	UK	CS	Multiple	Chronic urticaria	Moderate	Chronic	Yes	NR	Probable
Hampson JP et al.	UK	CR	Atorvastatin	Systemic hypersens. + eosinophilia	Severe	Weeks	Yes	NR	Probable

Author (Year)	Country	Design	Statin	Reaction	Severity	Time to onset	Resolution	Rechallenge	Causality
Anliker MD et al.	Switzerland	CR	Atorvastatin	Chronic urticaria	Moderate	Weeks-months	Yes	NR	Probable
Huertas AJ et al.	Spain	CR	Atorvastatin	Fixed drug eruption	Moderate	On re-exposure	Yes	Yes	Definite
Wong ITY et al.	Canada	CR	Rosuvastatin + Simvastatin	Drug eruption (cross-reaction)	Moderate	Weeks	Yes	Yes	Definite
Forouzan P et al.	USA	CR+Rev	Atorvastatin	Lichenoid eruption	Moderate	Weeks-months	Yes	NR	Probable
Rodriguez-Pazos L et al.	Spain	CR	NR	Photo-induced erythema multiforme	Moderate	After sun exposure	Yes	NR	Probable
Vasconcelos OM et al.	USA	CS	Multiple	Dermatomyositis-like syndrome	Severe	Weeks-months	Partial	NR	Probable
Goldberg I et al.	Israel	Obs	Multiple	Cutaneous reactions (various)	Variable	Variable	Possible	NR	Probable
Adams AE et al.	USA	CR	Simvastatin	Vesiculobullous/pustular eruption	Moderate-severe	NR	Yes	NR	Probable
El Mekki AB et al.	Morocco	CR	Simvastatin	Angioedema	Severe	NR	Yes	NR	Probable
Lacsamana JM et al.	USA	CR	Simvastatin (high-dose)	Angioedema	Severe	NR	Yes	NR	Probable
Cozzani E et al.	Italy	CR	Atorvastatin	Psoriasis exacerbation	Moderate	Weeks	Partial	NR	Probable

Author (Year)	Country	Design	Statin	Reaction	Severity	Time to onset	Resolution	Rechallenge	Causality
Gershovich OE et al.	USA	CR+Rev	Atorvastatin	Pruritus + hepatic dysfunction	Moderate	Weeks	Yes	NR	Probable

CR: Case report; CS: Case series; Obs: Observational; CR+Rev: Case report with review; NR: Not reported; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms.
Source: Elaborated by the authors (2026).

Spectrum, Frequency, and Severity of Reactions

The distribution of reaction types is presented in Table 2. Angioedema was the most frequently reported reaction (n=6; 24.0%), followed by drug eruptions (n=5; 20.0%), autoimmune/systemic reactions (n=4; 16.0%), lichenoid eruptions (n=3; 12.0%), pruritus (n=2; 8.0%), and chronic urticaria (n=2; 8.0%). DRESS syndrome, fixed drug eruption, photo-induced erythema multiforme, and psoriasis exacerbation each accounted for 4.0% of cases.

Regarding severity, 10 cases (40.0%) were classified as severe, 13 (52.0%) as moderate, and 1 (4.0%) as mild-moderate. Severe reactions were predominantly associated with angioedema (n=6), DRESS syndrome, systemic hypersensitivity, dermatomyositis-like syndrome, and acute hypersensitivity (n=1 each).

Table 2. Reaction types, frequency, severity, and resolution rates.

Reaction type	n (%)	Severe (%)	Complete resolution (%)	Main statin(s)
Angioedema	6 (24.0%)	6 (100%)	6/6 (100%)	Atorvastatin, Rosuvastatin, Simvastatin, Pitavastatin
Drug eruption (other)	5 (20.0%)	1 (20%)	5/5 (100%)	Atorvastatin, Rosuvastatin
Autoimmune/systemic	4 (16.0%)	3 (75%)	2/4 (50%)	Atorvastatin, Multiple
Lichenoid eruption	3 (12.0%)	0 (0%)	3/3 (100%)	Pravastatin, Simvastatin, Atorvastatin
Pruritus	2 (8.0%)	0 (0%)	2/2 (100%)	Rosuvastatin, Atorvastatin

Reaction type	n (%)	Severe (%)	Complete resolution (%)	Main statin(s)
Chronic urticaria	2 (8.0%)	0 (0%)	2/2 (100%)	Atorvastatin, Multiple
DRESS syndrome	1 (4.0%)	1 (100%)	1/1 (100%)	Rosuvastatin
Fixed drug eruption	1 (4.0%)	0 (0%)	1/1 (100%)	Atorvastatin
Photo-induced erythema multiforme	1 (4.0%)	0 (0%)	1/1 (100%)	NR
Psoriasis exacerbation	1 (4.0%)	0 (0%)	0/1 (partial)	Atorvastatin
TOTAL	25 (100%)	10 (40.0%)	22/25 (88.0%)	—

NR: Not reported; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms.
Source: Elaborated by the authors (2026).

Time to Onset and Clinical Outcomes

Time to onset was incompletely reported across included studies. Where available, onset was categorised as: immediate (<24h — n=1[5]); early (days to weeks — n=8); delayed (weeks to months — n=7); and chronic/recurrent (n=3). The case of acute hypersensitivity within 24 hours of the first atorvastatin dose suggests a pre-sensitised immune state. DRESS syndrome presented after 2–8 weeks,[6] consistent with its delayed-type mechanism.

Complete resolution after statin discontinuation was documented in 22 of 25 studies (88.0%). Partial resolution was reported in 2 cases — dermatomyositis-like syndrome and psoriasis exacerbation — both involving complex autoimmune mechanisms. Overall, resolution (complete or partial) was observed in 96.0% of cases, underscoring the paramount clinical importance of prompt drug withdrawal.

Positive rechallenge was documented in 3 cases (12.0%): recurrent angioedema upon re-introduction, fixed drug eruption at the same site, and cross-reactive eruption upon switching from rosuvastatin to simvastatin. These cases provide the strongest causal evidence available.

Causality and Immunological Mechanisms

Causality was classified as definite in 3 cases (12.0%) — all rechallenge-confirmed — and probable in 22 cases (88.0%), based on temporal association, resolution upon discontinuation, and absence of alternative explanations. Type IV (delayed-type) T-cell-mediated hypersensitivity was the predominant mechanism for lichenoid eruptions, DRESS, and fixed drug eruption. Histamine/bradykinin-mediated pathways were implicated in angioedema and urticaria. Drug-induced autoimmunity via anti-HMGCR pathways was described for dermatomyositis-like syndrome and lupus erythematosus tumidus. A photoallergic mechanism was proposed for photo-induced erythema multiforme.

Quality Assessment

JBI quality assessment results are presented in Table 3. All 22 case reports demonstrated adequate clinical description, described interventions, documented outcomes, addressed adverse effects, and provided clinically relevant information. The most consistent limitation was incomplete demographic reporting (Q1: Unclear in most reports). Overall, studies were of moderate to high quality.

Table 3. JBI Critical Appraisal results for included case reports.

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall
Pua VS et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Roger D et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Zgolli F et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Hanson K et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Pop M et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Oda T et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Trcko K et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Naz S et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Voloshyna D et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Shahbaz A et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Mustafa SF et al.	U	Y	Y	Y	Y	Y	Y	Y	High
Malik S et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Hampson JP et al.	U	Y	Y	Y	Y	Y	Y	Y	High
Anliker MD et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Huertas AJ et al.	U	Y	Y	Y	Y	Y	Y	Y	High

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall
Wong ITY et al.	U	Y	Y	Y	Y	Y	Y	Y	High
Forouzan P et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Rodriguez-Pazos L et al.	U	Y	Y	Y	Y	Y	Y	Y	High
Adams AE et al.	U	Y	Y	Y	Y	Y	Y	Y	High
El Mekki AB et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Lacsamana JM et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Cozzani E et al.	U	Y	Y	U	Y	Y	Y	Y	Moderate-High
Gershovich OE et al.	U	Y	Y	Y	Y	Y	Y	Y	High

Y: Yes; U: Unclear. Q1: Demographics; Q2: History; Q3: Baseline condition; Q4: Diagnostic tests; Q5: Intervention; Q6: Outcome; Q7: Adverse effects; Q8: Clinical relevance.
Source: Elaborated by the authors (2026).

Discussion

This systematic review identified 25 studies describing statin-associated allergic and cutaneous reactions, spanning a clinically diverse spectrum from mild pruritus to life-threatening angioedema and DRESS syndrome. To our knowledge, this is the first systematic review specifically focused on the allergic and cutaneous adverse effects of statins.

Atorvastatin was the most frequently implicated statin (40.0%), consistent with its global prescribing prevalence. Importantly, reactions were documented across all statin types — including a first reported case of angioedema with pitavastatin — suggesting a possible class effect rather than agent-specific toxicity. Cross-reactive drug eruption between rosuvastatin and simvastatin was documented, with direct clinical implications: switching to an alternative statin should be approached with caution.

The proportion of severe reactions (40.0%) is clinically significant and likely represents an underestimate given publication bias toward severe cases. Angioedema (24.0%) carries potential for airway compromise, and the DRESS syndrome case illustrates that statins can trigger potentially life-threatening systemic hypersensitivity. The overall resolution rate of 96.0% reinforces that prompt drug withdrawal is the cornerstone of management.

From a clinical standpoint, statins should be included in the differential diagnosis of unexplained urticaria, angioedema, lichenoid eruptions, and drug eruptions —

particularly in patients on long-term lipid-lowering therapy. The case of atorvastatin-induced drug eruption initially misdiagnosed as tinea cruris illustrates the diagnostic challenge these reactions can pose.

Limitations include the predominance of case reports, which are subject to selection and publication bias, and inconsistent reporting of demographic data, Naranjo scores, and time-to-onset information across included studies.

FINAL CONSIDERATIONS

Statins can induce a clinically diverse and potentially severe spectrum of allergic and cutaneous adverse reactions. Atorvastatin was the most commonly implicated agent, though reactions occurred across all statin classes, suggesting a possible class effect. Severe reactions accounted for 40.0% of cases, while resolution following drug discontinuation was observed in 96.0%, underscoring the paramount importance of timely recognition and prompt drug withdrawal.

Systematic pharmacovigilance studies, prospective registries, and standardised causality assessment are needed to better define the epidemiology and mechanisms of statin-associated cutaneous reactions. Until such data are available, clinicians should maintain a high index of suspicion and systematically report such cases.

PROSPERO: CRD420261391101 | Conflito de interesses: Nenhum | Financiamento: Nenhum

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SUPPLEMENTARY APPENDIX 1 — SEARCH STRATEGIES

PubMed/MEDLINE:

("statin"[tiab] OR "statins"[tiab] OR "HMG-CoA reductase inhibitor"[tiab] OR "atorvastatin"[tiab] OR "rosuvastatin"[tiab] OR "simvastatin"[tiab] OR "pravastatin"[tiab] OR "lovastatin"[tiab] OR "fluvastatin"[tiab] OR "pitavastatin"[tiab]) AND ("pruritus"[tiab] OR "prurigo"[tiab] OR "itching"[tiab] OR "urticaria"[tiab] OR "hives"[tiab] OR "angioedema"[tiab] OR "allergic reaction"[tiab] OR "hypersensitivity"[tiab] OR "skin rash"[tiab] OR "drug eruption"[tiab] OR "lichenoid"[tiab] OR "photosensitivity"[tiab] OR "anaphylaxis"[tiab] OR "cutaneous adverse"[tiab] OR "allergic dermatitis"[tiab])

Cochrane Library:

(statin OR statins OR "HMG-CoA reductase inhibitor" OR atorvastatin OR rosuvastatin OR simvastatin OR pravastatin OR lovastatin OR fluvastatin OR pitavastatin) AND (pruritus OR prurigo OR itching OR urticaria OR hives OR angioedema OR "allergic reaction" OR hypersensitivity OR "skin rash" OR "drug eruption" OR lichenoid OR photosensitivity OR anaphylaxis OR "cutaneous adverse" OR "allergic dermatitis")

LILACS/BVS:

(statin OR statins OR atorvastatina OR rosuvastatina OR sinvastatina OR pravastatina OR lovastatina OR fluvastatina OR pitavastatina OR "inibidor da HMG-CoA redutase") AND (prurido OR pruritus OR urticaria

OR angioedema OR "reacao alergica" OR "allergic reaction" OR hipersensibilidade OR hypersensitivity OR "erupcao cutanea" OR "drug eruption" OR anafilaxia OR anaphylaxis OR fotossensibilidade OR photosensitivity)

SUPPLEMENTARY APPENDIX 2 — REASONS FOR EXCLUSION AT FULL-TEXT ASSESSMENT

Table 4. Reasons for exclusion at full-text assessment.

Reason for exclusion	**n**
Reaction not caused by statin (other drug identified as causative agent)	4
No allergic or cutaneous reaction described in full text	3
Animal or in vitro study	2
Conference abstract without full data	2
Full text not available	1
Narrative review without original primary case data	1
Duplicate case report (less complete version)	1
Total excluded at full-text stage	14