MANEJO DE PACIENTES CON INTOLERANCIA A ESTATINAS: REVISIÓN SISTEMÁTICA DE LA LITERATURA

STATIN INTOLERANCE MANAGEMENT: A SYSTEMATIC REVIEW

TESIS PARA OPTAR POR EL TÍTULO PROFESIONAL DE MÉDICO CIRUJANO

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DEDICATORIA

Lina, Augusto y Mardy, los adoro con todo mi corazón. Gracias por ser mi soporte e inspiración en estos 7 años. Gracias por darme la oportunidad de convertirme en lo que siempre soñé.

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DECLARACIÓN DE CONFLICTO DE INTERÉS

- Los autores declaran no tener conflictos de interés.
- Los autores declaran que esta publicacion fue aprobada por Springer Nature con fecha de 14 de Noviembre de 2022

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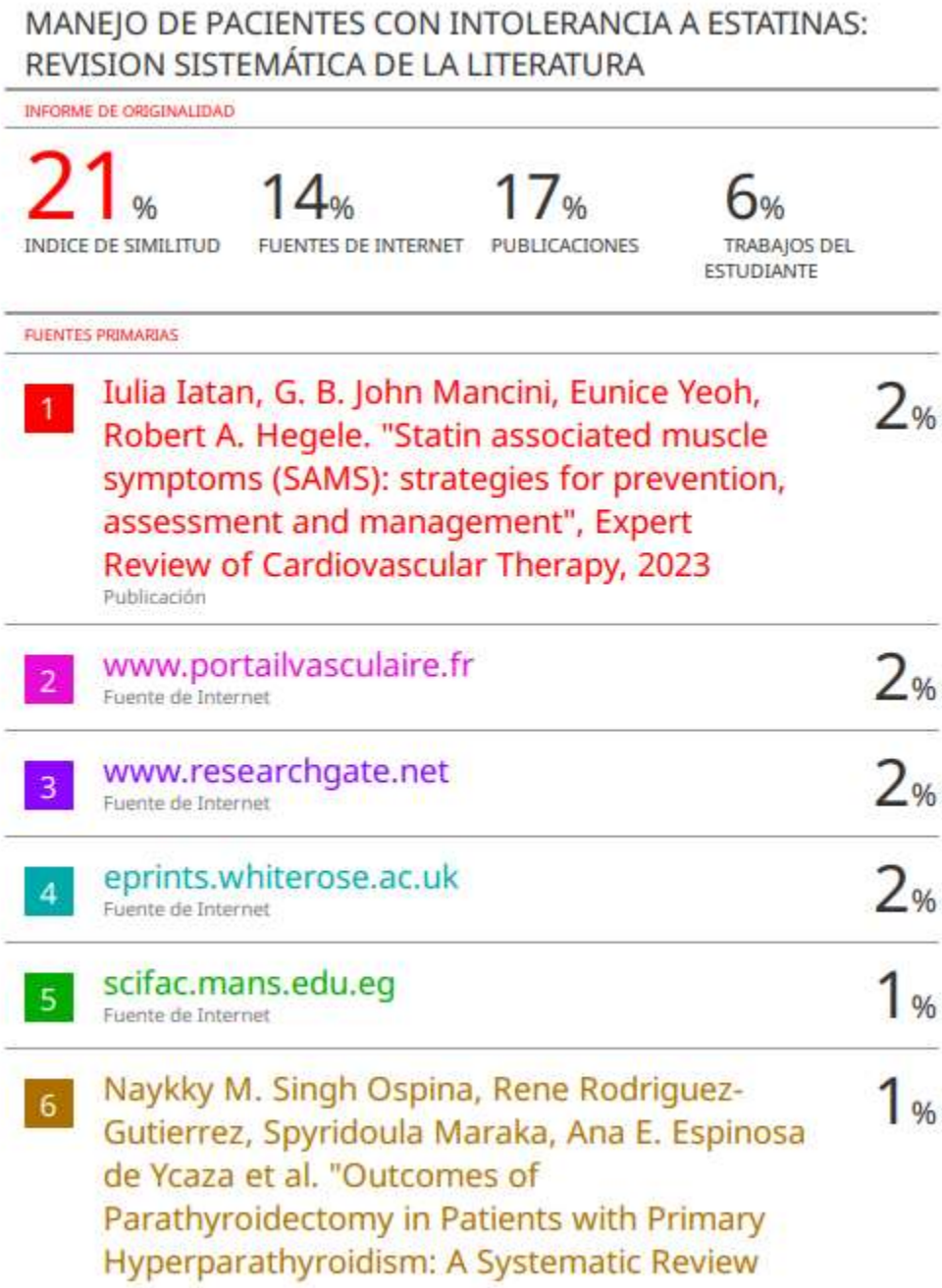

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TABLA DE CONTENIDOS

RESUMEN

Antecedentes: La intolerancia a las estatinas es un obstáculo importante en la prevención eficaz de la enfermedad cardiovascular aterosclerótica (ASCVD por sus siglas en inglés). Expertos no han reportado un consenso respecto a la definición ni a cómo abordar a este problema clínicamente. **Objetivo**: Caracterizar las diferentes recomendaciones de expertos sobre el cuidado de pacientes con intolerancia a las estatinas. **Materiales y Métodos**: Se realizo una revision sistemática registrada en PROSPERO, se buscaron artículos publicados en los últimos 5 años hasta el 1 de abril de 2022 en PubMed, EMBASE, Scopus, Cochrane, libros en línea, revisiones sistemáticas o pautas de práctica clínica, sin restricción de idioma. Los autores trabajaron en duplicado para extraer definiciones, recomendaciones de manejo y evidencia de apoyo citada. **Resultados**: Se identificaron 26 artículos elegibles, ninguno describió un método sistemático para resumir la evidencia o desarrollar y clasificar recomendaciones. De estos, 14 (54%) ofrecieron una definición de intolerancia a las estatinas. Se sugirió un enfoque secuencial para el manejo de la intolerancia a las estatinas en 24 (92%) de los artículos, describiendo 12 enfoques diferentes sin evidencia de eficacia. Investigar y descartar otras causas fue el primer paso más común. Todos los autores sugirieron volver reintentar el tratamiento con la misma u otra estatina después de un período de descanso. Pocos consideraron enfoques no lipídicos para reducir el riesgo de ASCVD y ninguno recomendó involucrar a los pacientes en la toma de decisiones compartida. **Conclusión**: Encontramos una variabilidad importante entre expertos respecto a la definición y el manejo de la intolerancia a las estatinas. Pocos se centraron en la reducción del riesgo de ASCVD y ninguno promovió la participación de los pacientes en la toma de decisiones compartida sobre cómo abordar la amenaza de ASCVD con o sin estatinas.

Palabras clave: estatinas, intoletancia, ASCVD, dislipidemia.

ABSTRACT

Background: Statin intolerance is a key barrier to the effective prevention of atherosclerotic cardiovascular disease (ASCVD). Experts do not agree on what it is and how to respond to this problem clinically. **Objective**: To characterize the range of expert recommendations about the care of patients with statin intolerance. **Methods**: Systematic review registered in PROSPERO that searched on April 1 2022 in PubMed, EMBASE, Scopus, Cochrane, online textbooks, and specialty textbooks for expert reviews (e.g., review articles and book chapters), systematic reviews, or clinical practice guidelines published in the past 5 years without language restriction. Authors working in duplicate extracted definitions, management recommendations, and supportive evidence cited. **Results**: We identified 26 eligible articles, none of which described a systematic method to summarize the evidence or to develop and grade recommendations. Of these, 14 (54%) offered a definition of statin intolerance. A sequenced approach to management of statin intolerance was suggested in 24 (92%) articles describing 12 different approaches without supporting evidence of efficacy. Investigating for other causes was the most common first step. All authors suggested rechallenging after a washout period with either the same or other statin. Few considered nonlipid approaches to reducing ASCVD risk and none recommended involving patients in shared decision making. **Conclusion**: We found substantial variability in the definition and management of statin intolerance among experts. Few focused on ASCVD risk reduction and none promoted the participation of patients in shared decision making about how to address the threat of ASCVD with or without statins.

Keywords: statins, intolerance, ASCVD, hypercholesterolemia

I. INTRODUCTION

Cardiovascular disease is the leading cause of death among adults in the United States [1]. Changes in diet, exercise, and medications, such as HMGCoA-reductase inhibitors or statins, can contribute to reducing this risk [2].

Patients benefit from using statins as these agents reduce both low density lipoprotein cholesterol (LDL-C) levels and the risk of major cardiovascular endpoints [3]. Adverse effects attributed to statins may prevent patients from using them regularly, a situation often referred to as statin intolerance [4]. These effects include but are not limited to myalgias, headache, dyspepsia, diarrhea, alopecia, erectile dysfunction, “brain fog”, fatigue, memory difficulties, and laboratory abnormalities (e.g., elevations in blood glucose, aspartate aminotransferase or creatine kinase levels) [5, 6]. By preventing the regular use of statins, statin intolerance leaves patients vulnerable to ASCVD [7].

A recent meta-analysis reported <10% incidence of statin intolerance [8], relying on strict definitions that exclude some patients who present in clinical practice unwilling to continue to take statins because of adverse effects. Also, an individual patient-data meta-analyses showed that muscle-related symptoms (muscle pain or weakness) were as common in trial participants receiving statins (27.1%) as in those receiving an indistinguishable placebo (26.6%) [9]. Regard- less of frequency or causality, clinicians must respond to patients unable to take statins because of adverse effects in ways that advance patient goals and priorities, including the prevention of ASCVD-related morbidity and mortality [10].

Experts have proposed algorithms and practice paths that clinicians can use to respond to this problematic situation. This review seeks to identify, characterize,

and appraise currently proposed strategies for the clinical management of statin intolerance in clinical practice. We sought to determine what are recommended strategies to manage statin intolerance in at-risk patients for whom statin therapy is recommended, and how confident can clinicians be that their patients will be better off if they were to follow these recommendations.

II. METHODS

The aim of the study was to systematically search, identify, and analyze expert recommended approaches to the management of statin intolerance in clinical practice. We sought to note differences and coincidences, and to characterize the strength of recommendation for either whole algorithms or individual pathway steps.

Protocol registration and guidelines

This systematic review was prospectively registered in PROSPERO [11] and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) [12].

Eligibility criteria

Eligible articles offered recommendations for the management of statin intolerance and were expert narrative reviews (e.g., review articles and book chapters), systematic reviews, or clinical practice guidelines published anywhere and in any language in the last 5 years. Eligible articles (a) described the clinical situation as statin intolerance or as discontinuation (or threat of discontinuation) of statins due

to adverse effects attributed to statins, and (b) offered a management strategy to address this problem in adults at any level of risk for ASCVD. After starting this review, we modified the protocol: we had planned to include only articles with an explicit definition of statin intolerance but, to be more inclusive, we removed this criterion.

Information sources and search strategy

An experienced reference librarian (E.K.V.) designed, in collaboration with study investigators, a comprehensive literature search of PubMed, EMBASE, Scopus, Cochrane Central Database of Systematic Review, online textbooks (UpToDate) and specialty textbooks, going back 5 years as of April 1, 2022. Two investigators (C.W., A.M.), working independently and in duplicate, screened abstracts and assessed potentially eligible full text reports for eligibility. Disagreements were resolved by consensus and arbitration by a subject matter expert (V.M.M.).

Data extraction and synthesis

We extracted characteristics of the included articles and the way they defined or described statin intolerance. To judge the confidence in the strategy proposed we appraised whether the authors conducted a systematic review of the evidence and followed an explicit guideline development process. We then extracted the strategy's reported goal, specific steps proposed (e.g., stop statin, offer same statin, offer alternative statin, offer other lipid lowering agent, calculate ASCVD risk, engage in shared decision making, measure creatine kinase) their type (e.g., education, communication, decision making, diagnostic, intervention, referral) and

sequence (e.g., before everything else, key branching step, next step). To understand the degree of confidence authors had that patients will be better off if the strategy proposed were followed, we planned to ascertain the evidence presented in support of the whole algorithm and/or for each key step, the level of trustworthiness, the outcomes measured and estimates (with measure of precision) of benefit and harmful effects. We compared the included strategies in terms of their problem definitions, goals, steps, sequence, and supportive evidence, when available.

III. RESULTS

Article selection

Figure 1 describes the flow of articles into our review. From titles and abstracts, we identified 76 articles for full text evaluation and 25 were considered eligible. The interviewer chance-adjusted agreement for eligibility at the full text level was k=0.88 (95% confidence interval 0.77–0.99), or near perfect.

During the writing of this report, i.e., outside of the range of our systematic search, experts from the National Lipid Association published an eligible article [4]. We added it to our review post hoc. The supplementary table describes each of the included articles, the definition of statin intolerance used, and the strategy proposed in each one.

None of the included articles described a systematic process to identify, review and synthesize the research evidence. Only one of the included articles described a process for the development and grading of their recommendations [13].

Statin intolerance definition:

Overall, 14 (54%) articles included a definition of statin intolerance. Most offered their own definitions, while 2 articles [14, 15] followed the European Atherosclerosis Society Consensus Panel [16, 17] or the recommendations from an international expert panel [17].

A simple definition of intolerance – statin therapy discontinued because of symptoms attributed to taking statins— was used by 3 (12%) articles [18–20]. Other definitions required intolerance to ≥ 2 different statins [4, 13–15, 21–25], abnormal test results [13, 15, 21, 22, 26, 27], and either muscle-related symptoms [24, 25, 27] or a broader range of symptoms [4, 13–15, 18, 19, 22, 26, 28–30].

Only 12 (46%) of the articles used a definition that required resolution of symptoms or laboratory abnormalities after statin discontinuation [4, 13, 15, 18, 21, 22, 24–26, 29, 31].

Management strategies

A stepwise approach for the management of statin intolerance was offered by 24 (92%) articles, which described 12 different strategies (***Table 1***). ***Figure 2*** describes the most reported steps and the sequence in which they were recommended.

The most common early step in these strategies, present in 39% of these, was the clinical exclusion of other causes for muscle symptoms otherwise attributed to statin use. Experts recommended excluding vitamin D deficiency, drug-drug interactions, intense exercise, hypothyroidism, and dermato- or polymyositis and other myopathies either as a primary cause of muscle symptoms or as factors that could increase the risk of statin-associated muscle symptoms.

The next most common early steps were the recalculation of cardiovascular risk and the quantification of creatine kinase levels ***(Fig. 2).*** These determinations could then be used to decide whether statin therapy could be continued, changed to a lower dose or to a different statin, or stopped (e.g., large elevations consistent with rhabdomyolysis). The use of other symptom assessment scores, such as the Statin-Associated Muscle Symptom Clinical Index, an instrument to ascertain the likelihood that patient symptoms are linked to statin use [32], was recommended by 6 (23%) articles.

All the reported strategies included rechallenging with a statin. Rechallenging was implemented, after a washout period of 2 to 6 weeks (wash out duration was not required or not reported in 13 (50%) articles) using low-dose statin (25 (96%) articles), taking long-acting statins on alternate days (20 (77%) articles), switching to another statin (24 (92%) articles), or taking a generic statin (1 (4%) articles).

Seven (27%) articles recommended maintaining the same statin therapy at the same dose without a wash-out period [18, 21–23, 30, 33, 34], when symptoms were tolerable and creatine kinase values were not severely elevated. Recommendations about the washout period duration were arbitrary. We found no justification offered for the duration of the recommended washout period (2 vs. 4 vs. 6 weeks).

When patients could not tolerate any statin after rechallenging, experts recommended switching to nonstatin lipid- lowering therapy (15 (58%) articles), namely ezetimibe (58%) or PCSK-9 inhibitors (50%). When patients could not tolerate sufficient statin therapy, experts recommended adding non- statin lipid-lowering drugs to the best-tolerated statin regimen (26 (100%) articles), namely ezetimibe (96%), PCSK-9 inhibitors (88%), or bile acid sequestrants (31%).

Thirteen (50%) articles [4, 13, 14, 18–20, 22, 25, 27–29, 35, 36] included re-evaluating ASCVD risk after statin discontinuation as an aid on how to proceed, or to evaluate whether the use of nonstatin therapies was sufficiently effective in reducing ASCVD risk. None of the articles considered reducing ASCVD risk through nonlipid pathways.

Most articles described the evidence of ASCVD risk reduction with recommended alternatives to the statin regimen the patient did not tolerate, but no article reported on the safety and efficacy of their management algorithm.

Patient education was recommended by approximately half of the articles (58%); no article recommended shared decision making.

IV. DISCUSSION

Our review of the expert literature published in the last 5 years regarding the definition and management of statin intolerance demonstrated large variation in definition and strategies without structured processes used to develop these recommendations and evidence to support the recommended strategies.

Our study, systematic in its approach, is limited in its scope as it includes mostly unsystematic narrative reviews from the last 5 years, although this correctly represents the degree of rigor and variation in expert recommendations in this area. While crafting this report, the NLA issued a statement on statin intolerance [4]. They propose defining statin intolerance as one or more adverse effects associated with statin therapy, that resolve or improve with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of statin or partial tolerance, with inability to tolerate the dose necessary to achieve the patient-specific

therapeutic objective. To classify a patient as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage. Considering ASCVD risk reduction, they favored re-assessing statin dose, changing statin and dosing schedule; and starting non-statin agents shown to be effective in randomized trials, if the therapeutic target were not achieved. In addition to offering a definition, this statement also cites the relevant evidence in support of its recommendations and focuses the strategy on achieving patient-important levels of ASCVD risk reduction.

Statin intolerance is only clinically important in patients in whom statin use is associated with reductions in ASCVD risk that patients value, such that their partial or completed statin discontinuation due to adverse effects renders these patients vulnerable to ASCVD events. This justifies strategies that review the need for ASCVD risk reduction and develop a remedial approach, commensurate with this risk, that considers the evidence-based role of statins, nonstatin lipid-lowering drugs, nonlipid-lowering drugs (e.g., antiplatelet agents, ACE inhibitors, GLP-1 receptor agonists), and other non- pharmacological interventions (e.g., smoking cessation, physical activity, Mediterranean diet) in reducing ASCVD risk [37].

Some of the approaches espoused in the included articles, however, narrowly focused on "using as high a dose of statins as tolerated for as long as possible" often without regard for the baseline ASCVD risk or the role of addressing other, nonlipid, modifiable ASCVD risk factors. A focus on ASCVD risk creates a path to involve patients in shared decision making to determine the extent and method to reduce ASCVD risk [37, 38].

Recent approaches can support shared decision making involving nonpharmacological and pharmacological interventions, including both lipid-lowering and nonlipid- lowering agents [38]. Shared decision making is a method of care based on a conversation and aimed at producing a care plan that is consistent with patient goals and is minimally disruptive of patient lives [39, 40]. The latter is cri- tical in the context of probable harm caused by deploying preventive care in asymptomatic individuals. That none of the included articles called for patient participation in shared decision making is a significant limitation of these expert recommendations.

Thus, our findings have important implications for research. Future work should focus on establishing (a) the value of ascertaining ASCVD risk when considering responding to statin intolerance, (b) the value of co-creating a preventive care plan that makes intellectual, emotional, and practical sense to patients using shared decision making to address all modifiable risk factors with effective lifestyle and pharmacological interventions, (c) the resulting ASCVD risk after a desirable, useful, and feasible regimen is achieved, and (d) how often statins – the same or a different regimen as the intolerable one – end up being part of that regimen.

This evidence should then influence future updates of well-developed and trustworthy clinical practice guidelines [41], designed to reduce the burden of cardiovascular dis- ease in this population. This evidence should also motivate payers to ease access to affordable medications shown effective in randomized trials in reducing ASCVD risk for patients who, being intolerant to statins, would benefit from intensive reductions in their ASCVD risk.

In conclusion, we have substantial variation in expert definitions of and recommendations to manage statin intolerance. Additional research should evaluate the efficacy of risk-based, patient-centered strategies to ASCVD prevention in patients who seem unable to tolerate statin therapy.

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46. European Society of Cardiology, 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 290, 140–205 (2019)

VI. TABLES AND FIGURES

TABLE 1. Definitions and proposed strategies

	n (%)
Offer a definition of statin intolerance	14 (56)
Offer a stepwise strategy	24 (92)
Strategies	
Exclusion of other causes of symptoms	23 (88)
Measure creatine kinase levels	16 (62)
Measure alanine transaminase levels	3 (12)
Supplement creatine	1 (4)
Measure vitamin D levels	10 (38)
Estimate symptom scores or use the SAMS-CI instrument	6 (23)
Recalculate ASCVD risk	14 (54)
Evaluate symptom severity	10 (38)
Stop statins	25 (96)
Maintain statins	7 (27)
Rechallenge with statins	26 (100)
Measure coronary artery calcium	1 (4)
Stop/maintain then:	
Use a lower dose	25 (96)
Administer on alternate days	20 (77)
Switch to another statin	24 (92)
Use a generic statin	1 (4)
Use same statin and dose	4 (15)
Switch to non-statin	15 (58)
Ezetimibe	15 (58)

Fibrates	4 (15)
PCSK-9 inhibitor	13 (50)
Bile acid sequestrant	5 (19)
Nutraceuticals	3 (12)
Bempedoic acid	2 (8)
Ion exchange resin	1 (4)
Adding non-statin drug	26 (100)
Ezetimibe	25 (96)
Fibrates	2 (8)
PCSK-9 inhibitor	23 (88)
Bile acid sequestrant	8 (31)
Bempedoic acid	5 (19)
Nutraceuticals	4 (15)
Coenzyme Q10	3 (12)
Phytosterols	1 (4)
Ion exchange resin	1 (4)
Patient education	15 (58)
Shared decision making	0 (0)

ASCVD, atherosclerotic cardiovascular disease; PCSK-9, proprotein convertase subtilisin/kexin type 9; SAMS-CI, Statin-Associated Muscle Symptom Clinical Index

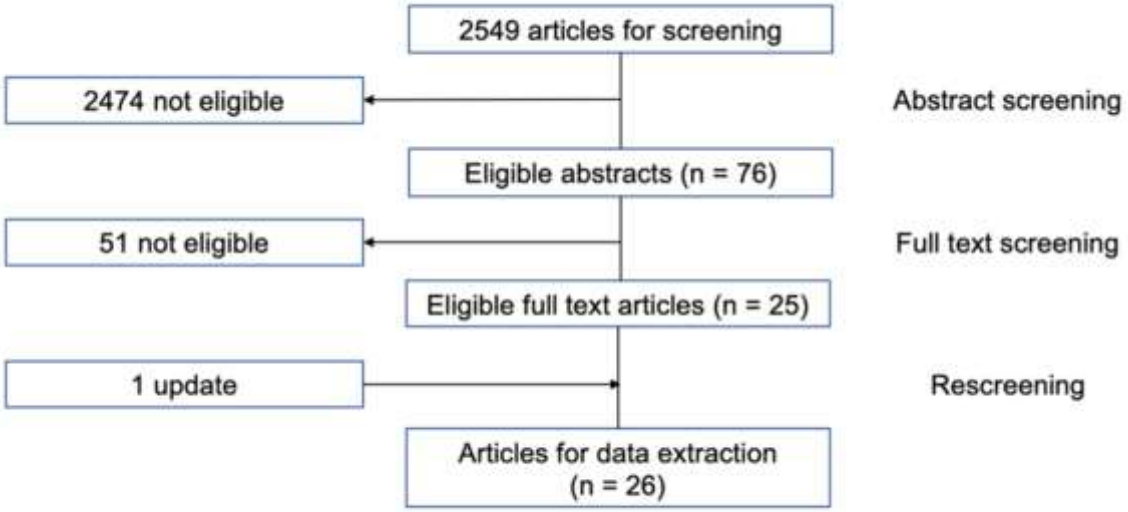

Fig. 1 Flowchart 1. Article selection process

FIGURE 2: Recommended approaches to address statin intolerance. The articles listed are organized by their recommended first step. The column tagged as 1st shows the first step recommended by each author included in this review, with subsequent steps appear in the next columns. For example, Chien et al, recommend starting with the exclusion of other causes of statin intolerance (SI), followed by calculation of cardiovascular (CV) Risk, and measure of creatine kinase (CK) levels, with washout and statin rechallenge depending on CK levels.

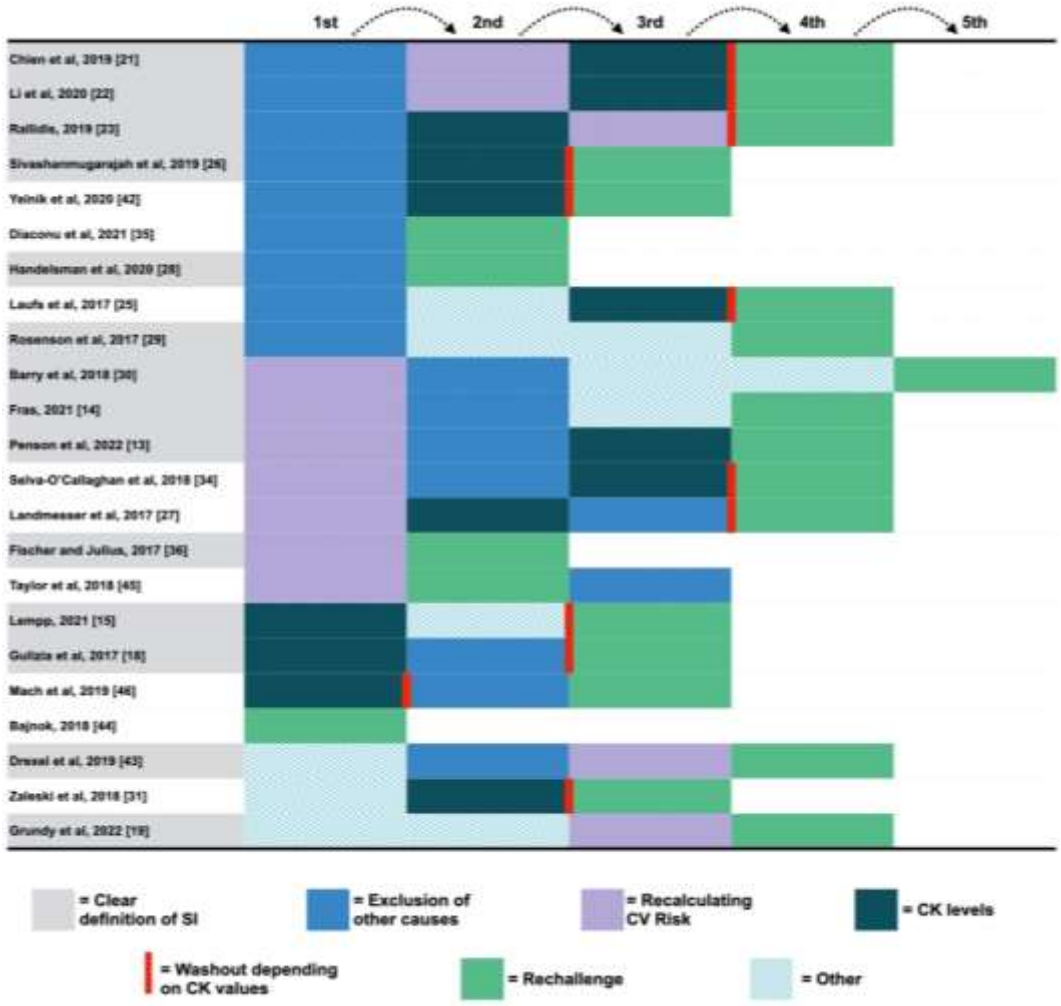

Table (Supplementary) – Description of included articles, methodology, definitions of statin intolerance, and management strategies

Publications	Definition of statin intolerance	Management recommendations for statin intolerance	Conducted systematic review / Rigorous method to develop recommendation described
Fras, 2021 [14]	Inability to tolerate ≥2 statins at their lowest daily doses, due to adverse subjective symptoms, with or without supplementary objective parameters	1. Exclude other causes of muscle symptoms 2. Build a personalized and comprehensive approach 3. Stop statin 4. Re-challenge to a low-dose statin and up titrate until maximal tolerated dose is established 5.If LDL-C goal is not achieved, add non-statin drugs - ezetimibe and/or PCSK9i	No / No
Laufs et al, 2017 [25]	Not offered	1.Exclude other causes of muscle symptoms and interactions 2. Build a personalized approach and take time for patient 3. Measure CK 3.1. If CK <4x ULN - Stop statins for 2 weeks - Re-challenge - If the symptoms reoccur, follow step 4 3.2. If CK>4x ULN: - Stop statins for 2-4 weeks and then follow step 4. Establish the highest tolerable statin dose and for that: - Start with very low dose - Change statin - Use potent statin - Consider alternate-day dosing 5. Aim to achieve LDL-C goal: - Use combination therapy with ezetimibe - Consider bile acid absorption inhibitor - Consider PCSK9i	No / No
Penson et al, 2022 [13]	Clinical syndrome whereby adverse effects associated with statin therapy [most commonly statin-associated muscle symptoms (SAMS) result in the discontinuation of therapy and consequently increase the risk of adverse cardiovascular outcomes.	1. Build a personalized intervention plan and calculate the individual`s current 10-year risk of CVC using a locally validated risk calculator 2. If patient presents adverse effects, measure CK and ALT and evaluate for possible and reversible causes: 2.1 No CK and ALT abnormalities and SAMS tolerable: measure SAMS-CI and if the result is > 6, consider switching statins, lowering dose, alternating days, or non-statin therapy. 2.2 If ALT >3 x ULN: reduce statin dose for 2-4 weeks and then rechallenge. 2.3. If CK>4 x ULN + Intolerable SAMS: stop statin for 2-4 weeks until symptom resolution and then rechallenge; add ezetimibe during the 2–4-week period if high-risk patient. 2.4. If CK >4 x ULN and no SAMS, stop statin until CK normalization and assess for other causes. 2.5. If CK>10 x ULN immediately discontinue and change to non-statin therapy that can include ezetimibe, bempedoic acid, nutraceuticals and PCSK9i. In all cases of rechallenge, if not tolerated at any dose, change to non-statin therapy.	No / Yes
Selva-O'Callaghan et al, 2018 [34]	Not offered	1. Review the indication for statin use in terms of cardiovascular risk 2. Exclude secondary causes of myopathy including physical activity related to the patient's signs and symptoms. 3. Measure CK levels 3.1 CK < 1000 IU/L and no muscle weakness: maintain the drug and monitor CK 3.2 CK 10x upper limit: clinician should clinician should assess the risk/benefits of drug withdrawal 3.3 Rhabdomyolysis: Withdraw the statin and do not administer it in the future and use approved effective drugs like PCSK9 inhibitors 4. Suspicious of self-limited toxic myopathy statin-induced autoimmune myopathy: Test for anti-HMGCR autoantibodies, consider muscle biopsy and manage according to the diagnosis (Drug withdrawal / Immunosuppressive therapy) 5. Use another statin OR a lower dose OR every other day schedule AND monitor CK levels and muscle strength OR use PCSK9 inhibitor	No / No
Sivashanmugarajah et al, 2019 [26]	1 Inability to tolerate a recommended statin dose to attain the desired CVD risk reduction due to symptoms, signs and/or biochemical tests potentially indicative of stain intolerance, which affects a patient's adherence to their prescribed statin. 2 Symptoms and/or biochemical abnormalities resolve with statin cessation (this may take days to weeks). 3 Symptoms and/or biochemical abnormalities recur with re-challenge to statin (this may take days to weeks). Ensure there are no contraindications to statin therapy (e.g., rhabdomyolysis) before re-challenge. 4 Items 1, 2 and 3 have been met for two different statins. 5 Prior to confirming a statin intolerance diagnosis, alternative explanations are excluded by a comprehensive history, examination, and relevant investigations.	1.History and examination 2.Consider differential diagnosis and exclude other causes 3. Measure CK 3.1. Withhold statin and review patient biochemistry in 2-3 weeks if CK <= 5 ULN and/or LFTs (liver functional tests) > 2x ULN and in 6-8 weeks if CK >= 5 - 10 ULN 4.Once asymptomatic and if no contraindication: rechallenge (lower dose of the same statin or different statin) and consider adding ezetimibe in higher vascular risk patients 5. If problems recur and/ or CK >5 x ULN: consider ceasing statin OR lower dose OR alternative statin OR every other day schedule 6.If able to tolerate statins but with muscle symptoms: discuss likely net benefit and consider continuing statins +/- simple analgesia 7.If completely unable to tolerate statins: use non statin medication to achieve lipid targets and/or reduce CVD risk (Ezetimibe, bile resins, PCSK9i, fibrate, high dose of Metamucil, policosanol containing foods and prescribed fish oils)	No / No (endorsed published algorithm)
Yelnik et al, 2020 [42]	Not offered	1. Exclude other causes 2.Measure CPK 2.1. If CPK <4N, stop statins 2 - 6 weeks - If symptoms persist, resume statin. - If symptoms improve, try a second statin - If symptoms reappear, try low dose statin, every other day dosing or twice a week. 2.2. If CPK >4N, stop statins for 6 weeks (until CPK normalizes and symptoms resolve. - Consider another low dose statin or every other day dosing or twice a week. 3. If LDL is higher than expected: add Ezetimibe. 4. If LDL is still higher than expected despite previous measures, add another molecule: fibrates, PCSK9.	No / No (endorsed 2015 EAS guidelines)

Rallidis, 2019 [23]	Intolerance to at least 2 different statins, one given at low dose.	1.Exclusion of secondary causes 2. Consider risk/benefits for statins, reassure patient for safety 3. Measure symptoms severity and CK levels 3.1. Moderate/severe symptoms: statin should be stopped regardless of CK levels. 3.2. Mild symptoms and CK levels <4 x ULN: statin can be continued with careful monitoring 3.3. Mild symptoms and CK levels >=4 x ULN without recent physical activity: statins should be stopped for 4-6 weeks 3.4. CK levels >10 x ULN and no symptoms: rhabdomyolysis should be considered, and statin should be stopped for 4-6 weeks 4. Once symptoms and CK normalized: reintroduction of a statin (usually a different one at a low dose) should be considered 5. If symptoms recurrence: 5.1. First recurrence: stop statin for 4-6 weeks. If they resolve, start 5 mg rosuvastatin or 5-10 atorvastatin on alternate days or twice weekly up to the maximum tolerated dose and add ezetimibe (+/- colesevelam) 5.2. Second recurrence: stop statin for 4-6 weeks. If they resolve, start ezetimibe (+/- colesevelam) 6. If LDL-C >100 mg/dl + CVD or >130 mg/dl in high risk after 4 weeks: add PCSK9 inhibitor	No / No (single-center approach)
Diaconu et al, 2021 [35]	Not offered	1. History and physical examination 2. Exclude other causes 3. Blood and urinary tests 4. Statin discontinuation 5. If symptoms resolve during the discontinuation: restart the same statin at a lower or other statin 6. If symptoms do not resolve during statin discontinuation: evaluate patients for other possible causes and reintroduce statins in optimal doses. 7. Treat with maximum dose of statin tolerated and add other drugs for lowering LDL-c if necessary, like ezetimibe, PCSK9i, bempedoic acid, and ANGPTL3 inhibitors, as well as nutraceuticals 8. In cases of complete statin intolerance, a non-statin regimen is recommended to lower LDL-C levels.	No / No
Lempp, 2021 [15]	The inability to tolerate at least two different statins done statin at the lowest starting average daily dose and the other statin at any dose, intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities, symptom or biomarker changes resolution or significant improvement upon dose decrease or discontinuation, symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognizes conditions increasing the risk of statin intolerance	1. Order a CK level 1.1 If CK level <4 x ULN: hold the medication for 2 to 4 weeks and perform SAMS-CI to assist and exclude secondary causes of myopathy. If symptoms resolve, restart statin at a lower dose and consider adding coenzyme Q10 100-200mg daily. 1.2. If CK level >4 x ULN or patient has severe muscle weakness: stop statin therapy for 6-8 weeks. If the symptoms continue after the stop, resume the statin at a lower dose and consider other causes of myopathy. If the symptoms resolve after the stop, start a lower dose of the same statin or a different one. 1.3. If CK level >10 x ULN: consider rhabdomyolysis, immediately discontinue statin therapy, diagnose with statin intolerance, and start on secondary non-statin therapy. 2. If SAMS returns a second time after restarting statin therapy, stop the statin and obtain another CK level. 2.1. If CK level <4 x ULN: consider intermittent dosing, decrease statin dose or consider another statin of different metabolism and add coenzyme Q10. If nothing works, prescribe secondary non-statin therapy. 2.2. If CK level >4 x ULN: stop statin therapy, after inability to tolerate 2 different statins diagnose the patient with statin intolerance and prescribe secondary non-statin therapy. 3. Always try to use the maximum tolerated dose of statin and other lipid lowering treatment to target LDL levels. Alternative non-statin monotherapy only if the patient has a TRUE statin intolerance 4. Non-statin options: - Medications with positive CV dual therapy outcomes: PCSK9i and Ezetimibe - Medications with CV outcomes to be determined: Bempedoic acid. - Medications with no evidence of improved CV outcomes: niacin, bile acid sequestrants, fibrates	No / No
Drexel et al, 2019 [43]	Not offered	1- It is important to distinguish between statin intolerance and non-adherence due to statin reluctance 2- Educational support from the healthcare provider is suggested 3- When adverse symptoms appear, check for causality. 4- Stratify patients according to their cardiovascular risk and personalize the treatment. 5- When an established and documented link between statin therapy and myalgia is set, the clinician is asked to re-challenge with a second statin. 6- If suspected statin intolerance is confirmed on statin rechallenge, other drugs are indicated with the use of a maximally tolerated statin dose to achieve guideline recommended LDL-C goals: - Combination therapy with ezetimibe. - Combination therapy with PCSK9i for high-risk CVD patients.	No / No
Fischer and Julius, 2017 [36]	Inability to tolerate at least three different statins (using three different metabolic pathways)	1.Choose a statin according to the extent of the necessary reduction of LDL cholesterol 2. When a statin intolerance is observed: reduce the dose, try a weaker statin or administer a potent statin less frequently 3. When no statin is tolerated (possibly also in combination with statins in low doses): start ezetimibe +/- bile acid sequestrants 4. When LDL-c target has not been reached: consider PCSK9i 5. Check the indication for lipoprotein apheresis according to LDL-C target value and/or Lipoprotein a with progressive vascular complications	No / No
Bajnok, 2018 [44]	Not offered	1. After a 2-to-4-week statin break: - Reintroduce the same statin again at a reduced or equal dose - Start another long-acting statin with a low dose and then titrated - Start a low-dose rosuvastatin or atorvastatin every 2 or 3, possibly every 7 days, followed by dose titration - Start lower dose of Fluvastatin or Pravastatin followed by dose titration 2. Ezetimibe monotherapy 3. Fibrate monotherapy	No / No
Grundy et al, 2022 [19]	Discontinuation of treatment due to perceived side effects.	1. Maximize control of other risk factors, combine lifestyle changes with drug therapies 2. Establish a competent management team, discuss risk and facilitate communication between clinician and patient, and establish routine follow-up and monitoring 3. Separate patients in two categories: WITH clinical atherosclerotic disease and WITHOUT atherosclerotic disease 3.1. WITH (high risk for cardiovascular events): - Challenge again with the same statin and dose. If it's not successful, try a different high-intensity statin and, if necessary, reduce the statin dose to moderate intensity. - Once statin alternatives are exhausted, an oral non-statin agent can be added to the tolerated statin dose such as ezetimibe, bile acid sequestrants and bempedoic acid. - If LDL < 70 mg/dL is not achieved with statins + oral non-statins, include a PCSK9 inhibitor 3.2. WITHOUT atherosclerotic disease: - If the coronary artery calcium is zero, there is no need to consider statin treatment for at least a decade - If the coronary artery calcium range of 1-99 Agatston units, statin therapy CAN be delayed for a decade, followed by rescanning, depending on the risk discussion between clinician-patient. - If the coronary artery calcium range of 1-99 Agatston units and the risk discussion favors LDL lowering a lower-intensity statin can be tried (fluvastatin XR 80mg daily or rosuvastatin 5mg daily or every other day). In addition, a non-statin can be started for example ezetimibe 10mg or bile acid - If the coronary artery calcium is equal or higher than 100 Agatston units a LDL lowering drug is preferred the same way as topic above. - If a patient with persistently severe hypercholesterolemia has rapidly advancing atherosclerosis by progressive coronary calcium, a PCSK9 inhibitor can be considered.	No / No
Rosenson et al, 2017 [29]	Not offered	1. Use SAMS-CI to measure patients' symptoms 1.1. If a low score is founded:	No / No

		- Exclude other causes and review patient history - Stop statin - After symptom resolution, initiate the same dose of the same statin or alternative high-intensity statin 1.2. If a high score is founded: - Exclude other causes and review patient history - Stop statin - After symptom resolution initiate a lower dose of the same statin or a alternative high-intensity statin - Readminister SAMS-CI: if still high score, initiate a statin with a different pharmacokinetic property and consider non-statin LDL-C lowering therapy	
Taylor et al, 2018 [45]	Not offered	1. Reassess the benefit of statin therapy: calculate CV risk, assess patient preference, and consider factors that may impact muscle symptoms 2. Confirm diagnosis (dechallenge and rechallenge with ≥ 2 statins) 3. Exclude other causes/ contributing factors 4. Reassure the patient 5. Try alternative statin and doses 6. Alternative treatment strategies: low-dose statins + ezetimibe, PCSK9i and other non-statin lipid lowering therapies	No / No
Barry et al, 2018 [30]	Goal-inhibiting statin intolerance (GISI) was introduced as a pragmatic way of defining statin intolerance. GISI was defined as a syndrome characterized by symptoms or biomarker abnormalities that prevent the long-term use of and adherence to indicated statin therapy, which includes a trial of at least 2 statins (including atorvastatin and rosuvastatin, as appropriate) and precludes reversible causes of statin adverse effects (e.g., drug interactions, untreated hypothyroidism)	1. Ensure valid indication for statin therapy 2. Identify risk factors for intolerance and check drug interactions 3. Patient education (risk and benefits of therapy) 4. Encourage nondrug therapies (dietary and exercise) and do not advocate for supplements to prevent statin-associated myopathy 5. Utilize a systematic challenge/dechallenge/rechallenge approach: evaluate clinical and laboratorial history, use modified version of symptom scores 6. Recommend non-statin therapy if necessary: addition of ezetimibe or a PCSK9i	No / No
Landmesser et al, 2017 [27]	Not offered	1. Identify muscle symptoms / measure CK levels (must be <10 x ULN) in very high risk patients 2. Counsel patient, look for risk factors or secondary causes 3. Statin washout of 2-6 weeks 4. Statin rechallenge with a second statin - If patient has no symptoms: continue statin and up titrate dose - If symptoms persist and CK >4 and <10 x ULN + LDL-C goal not achieved: ezetimibe 10 mg +/- bile acid sequestrant - If symptoms persist and CK ≤4 x ULN: try third low-dose statin - If none of these work, consider PCSK9i	No (based on 2015 EAS guidelines)
Gulizia et al, 2017 [18]	During statin treatment patient experiences unacceptable symptoms and/or laboratory alterations that are considered high risk. Both must be reversible and associated to statin therapy, discontinuation and rechallenge.	1.Measure CK 2.Exclude other causes of myopathy 3. If Mild-moderate asymptomatic or tolerable muscle pain and CK <5 x ULN: continue statin at same/lower dose, close follow-up 4. If CK level is >10 x ULN or rhabdomyolysis: discontinue therapy 5. If tolerable muscle pain and CK>5 x ULN or intolerable muscle pain: discontinue therapy 4.1. After statin stop, when symptoms disappear: check 2 CK levels + prescribe another statin at low dose (rechallenge) 4.2. If Symptoms and CK abnormalities reappear: low-dose rosuvastatin (2.5-5 mg) or rosuvastatin 5-10 mg or atorvastatin 10-20 mg on non-daily dosing. 4.3. If symptoms reappear: ezetimibe or fibrates (alone or in combination) 4.4 Unable to tolerate non-statin drugs: consider nutraceuticals or vegetable sterols alone or in combination	No / No
Chien et al, 2019 [21]	Statin intolerance should fulfill the following four criteria: (1) At least 2 statins are assessed for tolerability - one statin at the lowest starting daily dose and another statin at any daily dose; (2) Development of either objectionable symptoms or abnormal results of laboratory testing after statins; (3) The adverse effects are reversible upon statin discontinuation but reproducible by rechallenge; (4) Exclude other possible etiology. Additionally, any documented episode of statin-related rhabdomyolysis should be regarded as statin intolerance regardless of prior intolerant experiences.	1. Confirm causality 2.Identify and eliminate potential predisposing factors 3. Reassessing individuals risks and benefits 4. Evaluate patients' symptoms with the proposed scoring system and measure the CK levels -CK >10x ULN / rhabdomyolysis: withdraw statin, hydrate, and monitor renal function. Categorize these patients with statin intolerance and switch to non-statin therapies -CK levels 3-10x ULN: withdraw statins and restart after 2 CK levels return to normal, and symptoms resolve. Use reduced dose or start a different statin with a lower intensity 2-4 weeks after resolution of the events -CK levels < 3x ULN and no symptoms: reassess CK levels after 2-4 weeks and may continue the statin therapy 5. Non-statin therapies, including ezetimibe or PCSK9i could be used as a combination therapy to statin if lipid goal cannot be achieved under maximal tolerated statin dose or as a monotherapy if statins are intolerant.	No / No
Handelsman et al, 2020 [28]	Temporal association between statin initiation and symptom onset. Symptoms resolve with cessation of statin and recur with rechallenge with same and up to 2 alternative statins. 2 CK levels not needed to establish Dx but a CK elevation 4x ULN corroborates Dx. Also, if CK 10x ULN discontinue statin immediately and do not rechallenge.	1- Be aware of risk factors that may increase symptoms and exclude other causes: in these cases, consider using smaller statin doses and/or less potent statins with lower incidence of myopathy, along with cautious up-titration of dose. 2- Acknowledge patients' symptoms and consider stop statin. 3- When symptom resolve, if myopathy not severe, rechallenge: may try lower dose, less frequent dosing (1-3/week); different statin (at least 2; consider pitavastatin or fluvastatin) 4- Consider normalizing a low vitamin D and / or adding Coenzyme Q10 5- As needed, add non statin therapies CK level is not required for establishing the diagnosis, although it may be corroborated by CK ≥4 times the upper limit of normal. Cases of more severe myopathy leading to rhabdomyolysis, with CK >10 times the upper limit of normal requires immediate statin cessation, hydration, and monitoring of renal function. Its occurrence is a contraindication for future statin therapy.	No / No
Li et al, 2020 [22]	Must fulfill the following elements: 1.Clinical manifestations: either subjective symptoms or objective blood tests that are abnormal. 2.Types and doses of statins used: unable to tolerate ≥2 statins, where one of them is used at the lowest daily dose. 3. Temporal and causal relationships: adverse effects commence after the initiation or up-titration of statins, remit	1. Assess and confirm diagnosis: - -Measure CK - Supplement creatine - Exclude other causes and balance risk factors - Assess causality with SAMS-CI - Assess risk-benefit ratio 2. According to CK levels and symptoms, take next steps: - CK less or equal 10 x ULN + symptoms: Stop statins - CK>10x ULN: Stop statins - CK less or equal 5 x ULN + no symptoms: Continue statins - CK > 5x ULN and less or equal 10 x ULN + no symptoms: Stop statins	No / No

	upon discontinuation, and reappear after rechallenging. 4.Exclusion of other possible causes: there is a low possibility that the event is associated with other clinical conditions.	- CK >10 x ULN + no symptoms: Stop statins 3. Follow up and reassess CK levels and symptoms: - Resolved: Resume statins, reduce dose/frequency or switch - Maintain alterations: refer to specialist 4. If symptoms relapse, consider non-statin drugs: - Combine ezetimibe and/or PCSK9i with statins - Replace statins with non-statin lipid lowering agents - Complement treatment with non pharmacological managements	
Lloyd-Jones et al, 2017 [24]	Unacceptable muscle-related symptoms that resolve with discontinuation of therapy and occur with rechallenge on at least 2 to 3 statins, preferably ones that use different metabolic pathways and have different lipophilicity, and 1 of which is prescribed at the lowest approved dose	-Take a careful history -Rule out other causes and possible drug interactions -Discontinuation of statin therapy until resolution of the symptoms and subsequent rechallenge to verify recurrence of muscle-related symptoms. -Consider alternative dosing strategies: switch statins, lower dose, long half-life statins (atorvastatin, pitavastatin, rosuvastatin) 3 times per week or once per week - Non-statin therapies are not considered to be an alternative to evidence-based statin therapy unless statin intolerance has been systematically and rigorously evaluated and documented. - The ACC Statin Intolerance App is suggested for the comprehensive evaluation and management of potential statin-related side effects	No / No
Toth et al, 2018 [20]	Inability to tolerate a suitable dose of a statin required for a given patient's CV risk	-Look for other possible factors that may increase the risk of statin intolerance and try to identify true cases of statin intolerance -Rechallenging: lower dose, alternate-day therapy, consider changing from a hydrophilic to a lipophilic statin -Complete statin intolerance or tolerance only to low-to-moderate dose statin: consider ion-exchange resin, ezetimibe, and PCSK9i.	No / No
Zaleski et al, 2018 [31]	Not offered	1- Patient education on reversibility of symptoms 2- Measure CK concentrations 3- Measure vitamin D concentrations 4- Stop the statin until asymptomatic (failure of the symptoms to resolve after 2-3 months in patients with a normal CK argues against the statin cause of the symptoms) 5- Once asymptomatic: try the same statin at a lower dose or another statin 6- Combine lower dose statin with ezetimibe or use ezetimibe alone in patients unable to tolerate any statin 7- Try alternate dosing 8- Use other agents such as PCSK9i for patients that qualify for it 9- Occasionally recommend Coenzyme Q10 supplementation to patients associated or not with ubiquinone/ubiquinol	No / No
Newman et al, 2019 [33]	Not offered	- Establish good communication with the patient: the frequency of subjective adverse events can be strongly influenced by that. - Exclude other causes such as exercise, hypothyroidism, and measure vitamin D levels. - Stop statin treatment for 1 to 2 weeks and determine whether symptoms resolve. - Check CK levels: - If CK is elevated >10 times the ULN (or >5 times the ULN in a vulnerable patient): the statin should be stopped immediately. - If CK is considerably elevated and the patient is at risk of acute renal failure based on the CK level and presence of comorbidities: hospitalization might be required. - If CK is moderately elevated (e.g., between 3 and 4 times the ULN), and the symptoms are mild: the statin can be continued, with another measurement in a few days. - If the CK concentration is falling or stable: the statin can be continued, with further follow-up depending on the CK level, symptoms, and medical history - After statin discontinuation, if the symptomatology and laboratory abnormalities do not improve the patient should be referred to a muscle specialist to consider other diagnoses such as polymyalgia rheumatica, mitochondrial myopathies and the very rare statin-associated autoimmune myopathy (or immune-mediated necrotizing myopathy). - The rechallenge is usually done at a lower dose, or with an alternative statin, given daily or several times a week.	No / No
Mach et al, 2020 [46]	Not offered	1.Access CV risk 2.Measure ALT before treatment (routine control thereafter is not recommended unless symptoms suggest liver disease) -If ALT <3 x ULN: continue therapy and recheck enzymes in 4-6 weeks -If ALT ≥3 x ULN: stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4-6 weeks -If ALT returned to normal, cautious reintroduction may be considered -If ALT remains elevated, check other reasons 2.1 Measure CK before starting therapy (routine control is not necessary unless patient develops myalgia) -If CK is >4 x ULN, do not start drug therapy and recheck 2.2 HbA1c or glucose should be considered in patients at high-risk of developing diabetes and on high-dose statin treatment 3.Define treatment goal and use a high potency statin at high recommended/tolerable dose to reach the goal 4.If patient presents muscle symptoms: -Symptomatic and CK <4 x ULN: 2-4 weeks washout of statin followed by statin rechallenge and checking for other causes of muscular symptoms if they persist OR by starting a second statin at usual dose if symptoms improve -If CK ≥4 x ULN: 6 weeks washout until normalization of CK and symptoms followed by low-dose third potent statin that can be given in alternate day or once/twice weekly dosing regimen 5.If the goal is reached, follow up annually or more frequently if indicated 5.1 If the goal is not reached, add ezetimibe 6. If the goal with statin + ezetimibe is not reached, add PCSK9 inhibitor for secondary prevention in very-high-risk patients and for primary prevention for patients with familiar hypercholesterolemia (FH) + another major risk factor and in individuals at very-high risk but without FH 7.Consider adding bile acid sequestrant	

ANGPTL3, angiopoietin like 3; ALT, alanine transaminase; CK, creatine kinase; CVD, cardiovascular disease; HMGCR, 3-Hydroxy-3-Methylglutaryl-CoA Reductase; PCSK9i, PCSK-9, proprotein convertase subtilisin/kexin type 9 inhibitors; SAMS-CI, Statin-Associated Muscle Symptom Clinical Index; ULN, upper limit of normal