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Prescribing statin therapy in physically (in)active individuals vs prescribing physical activity in statin-treated patients: A four-scenario practical approach

Blanca Gavilán-Carrera [a,b,c,d], Alberto Soriano-Maldonado [e,f,*], Juan Diego Mediavilla-García [a], Carl J. Lavie [g], José Antonio Vargas-Hitos [a,b]

[a] Department of Internal Medicine, Virgen de las Nieves University Hospital, Granada, Spain
[b] Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain
[c] PA-HELP "Physical Activity for HEaLth Promotion" Research Group, University of Granada, Granada, Spain
[d] Sport and Health University Research Institute (iMUDS), University of Granada, Granada, Spain
[e] Department of Education, Faculty of Education Sciences, University of Almería, Almería, Spain
[f] SPORT Research Group (CTS-1024), CIBIS (Centro de Investigación para el Bienestar y la Inclusión Social) Research Center, University of Almería, Almería, Spain
[g] Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-the UQ School of Medicine, New Orleans, LA, USA

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ABSTRACT

Statins are among the most commonly prescribed medications worldwide. Statin-associated muscle symptoms (SAMS) represent a frequent statin-related adverse effect associated with statin discontinuation and increased cardiovascular disease (CVD) events. Emerging evidence indicate that the majority of SAMS might not be actually caused by statins, and the nocebo/drucebo effect (i.e. adverse effects caused by negative expectations) might also explain SAMS. Physical activity (PA) is a cornerstone in the management of CVD risk. However, evidence of increased creatine-kinase levels in statin-treated athletes exposed to a marathon has been generalized, at least to some extent, to the general population and other types of PA. This generalization is likely inappropriate and might induce fear around PA in statin users. In addition, the guidelines for lipid management focus on aerobic PA while the potential of reducing sedentary behavior and undertaking resistance training have been overlooked. The aim of this report is to provide a novel proposal for the concurrent prescription of statin therapy and PA addressing the most common and clinically relevant scenarios by simultaneously considering the different stages of statin therapy and the history of PA. These scenarios include i) statin therapy initiation in physically inactive patients, ii) PA/exercise initiation in statin-treated patients, iii) statin therapy initiation in physically active patients, and iv) statin therapy in athletes and very active individuals performing SAMS-risky activities.

1. Introduction

Statins are among the most commonly prescribed medications worldwide [1]. These drugs are used to reduce lipid levels and cardiovascular disease (CVD) risk in both primary (patients with hypercholesterolemia) and secondary (patients with a history of myocardial infarction, stroke, or peripheral artery disease) prevention [2]. Although statin therapy is generally very effective and well-tolerated, statin-associated muscle symptoms (SAMS) represents a frequent [3] statin-related adverse effect [2]. The incidence of SAMS is estimated between 1.5% and 5% in randomized trials and 10–33% in observational studies [4]. The clinical features of SAMS range from harmless muscle symptoms (the most common) to very-rare life-threatening rhabdomyolysis [5]. There is no diagnostic test to determine whether muscle symptoms are directly attributable to statins, and the diagnosis of SAMS is based on i) the exclusion of potentially alternative causes and ii) the

Abbreviations: ACSM, American College of Sports Medicine; CK, Creatinine Kinase; CV, Cardiovascular; CVD, Cardiovascular Disease; ESC/EAS, European Society of Cardiology / European Atherosclerosis Society; LDL-C, Low-density Lipoprotein-Cholesterol; PA, Physical Activity; SAMS, Statin-associated Muscle Symptoms; SB, Sedentary Behaviors; WHO, World Health Organization.

* Corresponding author at: Department of Education, Faculty of Education Sciences, University of Almería, Almería, Spain.
E-mail address: asoriano@ual.es (A. Soriano-Maldonado).

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temporal association with discontinuation and response to statin re-challenge [5]. This diagnosis is frustrating for patients [6] and difficult to distinguish from the nocebo effect (i.e. adverse effects caused by negative expectations of harm) [3], which partially explains SAMS in many cases [7]. Indeed, recent high-profile publications revealed that the majority of SAMS might not be actually caused by statins [8,9] and confirmed its general safety on muscle [10]. The latest evidence also suggests that the most commonly prescribed statin and dosage (atorvastatin at intermediate dose) is better tolerated than other statins (simvastatin and pravastatin) at equivalent doses [10]. There are other theories regarding the molecular mechanisms that induce SAMS that remain up for debate [11]. Regardless of their etiology, probably multifactorial [12], symptoms experienced by patients while taking statins are real and need to be acknowledged [12]. SAMS are currently considered a major health concern because they are associated with statin discontinuation [13] and, consequently, high rates of CVD events [14].

In the management of statin-treated patients, clinicians must rule out or identify predisposing factors to SAMS [12], and consider both muscle symptoms along with creatinine kinase (CK) levels to adjust statin therapy (reduce statin dose or switching statins) [3,5]. Others consider, however, that the muscle symptoms are not to be considered when adjusting the treatment because many times they represent a nocebo/-drucebo effect [9], and suggest these decisions should be exclusively based on CK levels. Notwithstanding, this approach overlook patients' perspectives which might, along with clinician-related factors, influence statin use [6] and should be taken into account for a shared decision process [6]. Provider-patient communication around statins seem to be inadequate [15], this affecting to their use and side effects [6]. Improving the patient-clinician communication can: i) prevent the nocebo/drucebo effect by emphasizing the benefits of statins over their side effects [12], ii) adjust the preconceived notion and misinformation around statins [6,14], and iii) increase the patients' adherence to treatment [14]. A summary of strategies proposed by different expert societies [12, 16] for SAMS prevention and management is presented in Table 1.

Before statin prescription, the international guidelines from European [2] and American [17] societies encourage the inclusion of lifestyle advice to reduce cholesterol levels [2]. Even when pharmacological therapy is finally needed, physical activity (PA) remains a cornerstone in the management of CVD risk [18]. However, the guidelines for lipid management [2,17] are entirely focused on aerobic PA while resistance training, despite its wide benefits for cardiovascular (CV) health [19], has been completely overlooked [20]. In addition, these guidelines also omit the potential of reducing sedentary behaviors (SB; i.e. too much sitting), which is strongly detrimental for CV health [21]. Although high volumes of moderate-to-vigorous PA may attenuate the CVD risk associated with excessive SB [22], achieving the required duration and intensity of PA is difficult, particularly for highly sedentary or inactive patients. Consequently, the emphasis on moderate-intensity aerobic PA could have limited benefits in clinical settings, especially in the absence of structured supervision and instruction [23]. In this regard, novel approaches advocate for starting by reducing SB as an initial step in a gradual approach that can progress towards PA of varying intensity and exercise counseling [21,23].

Despite its widely-known benefits for CVD protection, PA has also been suggested as a predisposing factor to SAMS [24] due to the potential exercise-induced muscle damage. Exercise-induced muscle damage, indirectly measured by CK levels, is a complex process affected by age, sex, fitness level, intensity, duration, and type of activity, among other factors [25]. However, it seems that the evidence of increased CK levels in a specific population performing a specific PA type (i.e., statin-treated athletes exposed to a marathon) has been generalized, at least to some extent, to the general population and other types of PA [26, 27]. This generalization is likely inappropriate and might induce fear around PA both in clinicians and in statin users [28]. Indeed, PA has

Table 1
Considerations for SAMS prevention and management under different scenarios.

Considerations for SAMS prevention and monitoring
Exclude, be alert of, and treat (if needed) predisposing factors, such as[12]: • Demographics: age > 75, female sex, Asian ethnicity, lower body weight • Genetics: family history of SAMS, pathogenic variants in statin-related genes • Comorbid conditions: hypothyroidism, vitamin D deficiency, musculoskeletal disease, immunologic disease, chronic kidney disease, organ or electrolyte dysfunction • Social: alcohol use • Drugs: fibrates, colchicine, immunosuppressants, antiarrhythmics, antivirals, antibiotics, antifungals, antiseizure, and others. • Physical activity: professional athletes and individuals performing SAMS-risky physical activities (extensive or high intensity exercise, hypertrophy training or activities with an high eccentric component). • Improve communication with patients considering their perspectives around statins in a shared-decision process[6]. • Educate patients on the nocebo effect while emphasizing benefits and the safety of statins[12].
Measure baseline CK levels: • CK > 4 times Upper Limit of Normal (ULN): do not start statin, look for causes of CK elevations and recheck
In physically active individuals (especially professional athletes and those performing SAMS-risky physical activities), measure baseline CK levels 48 h after the activity is performed[16]. • CK monitoring: o 4–6 weeks after statin initiation o 4–6 weeks after exercise initiation in statin-treated individuals • If a SAMS-risky activity is planned: a reduction of statin dose (or even therapy discontinuation) for at least 2 days before could be considered. This decision should be balanced with the risk of discontinuing statins[16].
Considerations for SAMS management
Scenario 1: statin initiation in physically inactive patients [2]: o CK < 4 times ULN without symptoms: acceptable. Periodic monitoring. o CK < 4 times ULN + symptoms: symptoms and CK should be monitored[2], and temporal discontinuation of statins for 2–4 weeks is recommended when muscle symptoms are persistent and limiting. o CK levels > 4 times ULN: o Muscle symptoms persistent and limiting: temporal discontinuation* of statins for 6 weeks o No presence of muscle symptoms: statins should be continued with CK monitoring between 2 and 6 weeks. o CK levels > 10 times ULN: statins should be stopped* , renal function checked, and CK monitored every 2 weeks.
Scenario 2: physical activity/exercise initiation in statin-treated patients [16]: o CK levels < 4 times ULN without symptoms: PA/exercise duration and intensity could be increased. o CK levels < 4 times ULN with symptoms or CK elevations due to PA/exercise: consider individual CV risk and reduce PA/exercise duration and intensity and avoid SAMS-risky activities in high or very high-risk patients. o CK levels 4–10 times ULN: If PA/exercise is excluded as the main cause: discontinue statins* and reduce exercise. o CK levels > 10 times ULN: If PA/exercise is excluded as the main cause: discontinue statins* and exercise, and CK monitored every 2 weeks. * Temporal discontinuation should be followed by statin re-challenge with a different statin type, lower doses, alternate day regimes, or finally combined with non-statin lipid-lowering therapy (ezetimibe, PCSK9 inhibitors, or bempedoic acid options [60]) if needed.
Scenario 3: statin initiation in physically active patients for health[16]: o Recommendations on how to manage SAMS mirror those proposed for scenario 2. o Consider modifications in physical activity dose (reducing duration and intensity, avoid hypertrophy and eccentric training) when initiating statin therapy.
Scenario 4: Statin initiation on athletes and individuals performing SAMS-risky activities o Recommendations on how to manage SAMS mirror those proposed for scenario 2. o The balanced decision on reducing or temporarily discontinuing statins according to the CV risk could be of the applicable. For non-professional athletes, the decision of reducing statin therapy and intensity and type of exercise should be carefully balanced.

CK: creatine kinase; CV: cardiovascular; SAMS: statin-associated muscle symptoms; ULN: Upper Limit of Normal;

recently demonstrated to counteract statin-induced adverse effects in skeletal muscle [29,30]. Overall, a more comprehensive understanding of the concurrent prescription of statin therapy and PA is of wide scientific and clinical interest. The aim of this report is to provide a novel proposal for the concurrent prescription of statin therapy and PA addressing the most common and clinically relevant scenarios by considering the different stages of statin therapy (i.e. initiation or continuation) and the history of PA (i.e. inactive, active or professional athletes), which might differently influence the development and prognosis of SAMS [16].

2. Statin therapy initiation in physically inactive patients (scenario 1)

A physically inactive person is someone who do not meet the World Health Organization (WHO) recommendations on PA (150–300 min/week of moderate PA or 75–150 min of vigorous PA plus 2 days/week of muscle-strengthening activities) [31]. Given that 4 out of 5 adults do not meet the combined aerobic and muscle-strengthening activities recommendations [32], this scenario likely applies to a large percentage of individuals attending clinical settings. The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemias proposed that all patients should receive lifestyle advice (always) and pharmacological treatment (if needed) [2] according to their global CVD risk as follows:

For patients at moderate CVD risk, the ESC/EAS proposed to include lifestyle changes first and, subsequently, pharmacological treatment when low-density lipoprotein cholesterol (LDL-C) goals are not achieved with lifestyle changes alone [2]. Lifestyle recommendations regarding PA only include "*30–60 min/day of moderate-to-vigorous PA*" [2]. In this regard, we suggest that PA should be gradually increased to allow the adaptation of the body systems to exercise-related changes, particularly in inactive individuals [23]. Emerging evidence for CVD prevention and management [21] propose to shift the initial focus from PA counseling towards reducing SB and progressively replacing sedentary time with activities of light intensity [23]. The "*Sit less and move more"* initial stage represents a more feasible and graduated approach to improve CV health [23]. Despite these benefits, clinicians face many barriers to include PA recommendations, among which stands out the lack of time and medical training in this matter [33]. Improving curricula of medical schools to educate and empower future clinicians [33] and using models of continued education [34] is needed to overcome these knowledge-related barriers. In this regard, different studies [21,23] and initiatives such as *Exercise Is Medicine* by the American College of Sports Medicine (ACSM) [34,35] provide resources and specific strategies ("https://www.exerciseismedicine.org/eim-in-action/health-care/resources/rx-for-health-series/") to help clinicians integrate general and disease-specific PA recommendations into their clinical practice [36]. Once SB is reduced, progressing towards increasing PA and (thereafter) personalized exercise training programs will provide further health benefits by increasing physical fitness [37]. Clinicians might find even more difficulties at this stage, as it has been recently evidenced that they provide too heterogeneous exercise prescriptions for CVD prevention with low agreement with international recommendations [38]. In addition to improve health professionals' education, clinicians should consider referring patients to exercise professionals that, following the recommendations of international scientific associations (for instance: ACSM's guidelines [36]), will adapt exercise parameters (type, frequency, duration, intensity) to patients with dyslipidemia. Finally, undertaking 3 days per week of moderate-intensity aerobic and resistance exercise before statin treatment could counteract statin-induced adverse effects in muscle [30]. Therefore, PA could be a promising strategy, not only to avoid the need of pharmacological treatment for hypercholesterolemia but also to improve treatment tolerance if statin therapy is finally needed.

For patients at high/very high CVD risk, the ESC/EAS proposed to include lifestyle intervention (including at least 30 min/day of moderate-to-vigorous PA) plus concomitant pharmacological treatment from the beginning [2]. It is worth noting that the initiation a new routine of PA could be a reason for temporary muscle pain [16], specially without a proper adaptation period. The simultaneous initiation of moderate-to-vigorous PA along with statins could hinder the identification of the cause of potential muscle pain. In addition, a previous trial conducted in sedentary obese individuals who simultaneously initiated statins and aerobic exercise showed that statin therapy attenuated the increases in cardiorespiratory fitness and skeletal muscle mitochondria [39], although changes in muscle symptoms were not assessed. Therefore, in these cases, our suggestion is that the first-line conservative approach could include a combination of pharmacological therapy with a reduction of sedentary behavior to enhance the CVD protection. Once the LDL-C goal is achieved and pharmacological treatment is stable (scenario 2), these patients could progressively progress through PA counseling and (thereafter) an individualized exercise program supervised by exercise specialists following the aforementioned international guidelines [18,36]. The benefits of including exercise in statin-treated patients are discussed in scenario 2. Our proposal on how to combine PA counseling and exercise prescription in physically inactive patients that initiate statins is schematically shown in Fig. 1.

3. Physical activity /exercise initiation in statin-treated patients (scenario 2)

Individuals who receive statin therapy can increase their CVD protection initiating a PA/exercise program. A recent meta-analysis [30] concluded that exercise combined with statin therapy, compared to statin therapy alone, improved insulin sensitivity, inflammation, and physical fitness, with no changes in lipid concentrations [30]. These results are of particular interest because physical fitness is a marker of CV health strongly associated with lower mortality risk in statin-treated individuals [40] and fitness might only be improved with exercise. Exercise also reduces the potential diabetes-onset related to statin therapy in statin-treated patients [41]. The systematic review by Gui et al. [30] also examined the safety of exercise combined with statin therapy and showed that acute high-intensity aerobic and resistance exercise (i.e. a marathon or bouts of maximum eccentric contractions), as well as acute moderate-intensity aerobic activities with an eccentric component (downhill walking 15% incline on a treadmill), might increase muscle pain and CK levels, or decrease muscle mass. It seems therefore clear that high-intensity and eccentric activities are not appropriate to start with for statin-treated patients. By contrast, chronic aerobic and resistance exercise of moderate intensity seem to attenuate CK elevations and improve muscle function [30]. It must be noted, however, that Gui et al. [30], combined mice and humans, athletes and sedentary individuals, statin-naive and statin-treated patients under different doses of statin therapy in the same analyses and the results are likely to differ for subjects with different characteristics. The safety and efficacy of engaging in aerobic PA and muscle strength for statin users has been, however, confirmed in subsequent systematic reviews [28]. Despite the potential risks of very vigorous and eccentric exercise, the benefits of engaging in PA while on statin therapy largely outweigh the risks [28]. Based on the above, we propose that the physician's initial advice could be to reduce sedentary behavior and progressively increase PA volume and intensity, according to the patient's tolerance, the response to statin therapy, muscle symptoms and CK changes, with the ultimate goal for patients to engage in an exercise program of moderate-intensity aerobic and resistance training 3 days/week [29,30]. The available evidence, however, is insufficient to provide specific recommendations regarding the duration of exercise or other activity types (i.e. flexibility training) for statin-treated individuals. In this sense, physicians should consider refer patients to exercise specialists who will prescribed individualized based on exercise parameters (type, frequency, duration, intensity) [36],

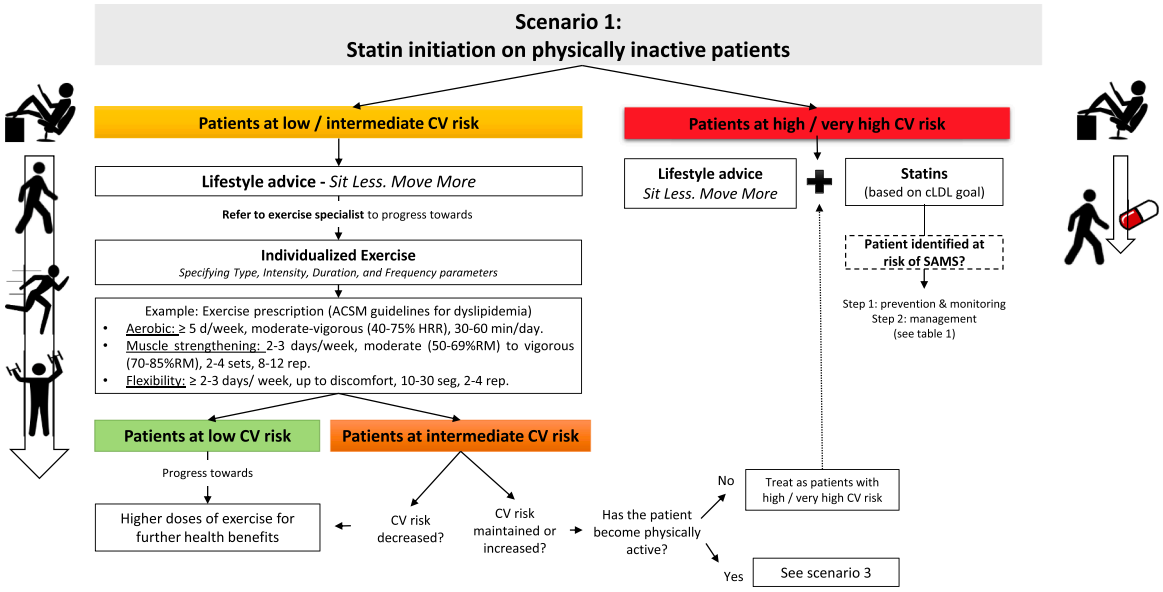

Fig. 1. Scenario 1: Statin therapy initiation in physically inactive patients.

starting with the most conservative ranges in these cases. In terms of SAMS prevention, patients presenting with relevant risk factors for developing SAMS (Table 1) should be identified. Also, monitoring muscle symptoms and, checking CK levels 4–6 weeks after PA/exercise initiation is recommended [16]; when possible, checking CK levels 48 h before beginning PA may be of interest. Some strategies could be implemented to minimize the increases in muscle symptoms and CK levels as a result of exercise: to include a familiarization period for the patient to get used to the new activities (sedentary individuals evoke greater CK increases following resistance exercise), to reduce the intensity, to increase resting periods, or to avoid slow concentric contractions at high intensity which could result in higher muscular damage [42]. A scheme for the application of this approach is presented in Fig. 2.

4. Statin therapy initiation in physically active patients (scenario 3)

A physically active person is someone who meets the WHO PA guidelines [31]. In their recent position paper [16], the International Lipid Expert Panel (ILEP) supported the 2019 ESC and EAS acknowledgment of higher possibility of muscle symptoms and CK elevation when statin therapy is initiated in individuals performing regular moderate to vigorous PA. However, the spectrum of activities included ranged from the lower limit of moderate PA, that is known to improve CV health [31] and might protect against SAMS [29,30], to the higher limit of vigorous or extensive PA (e.g. professional athletes), which might imply a much higher risk of SAMS development due to the

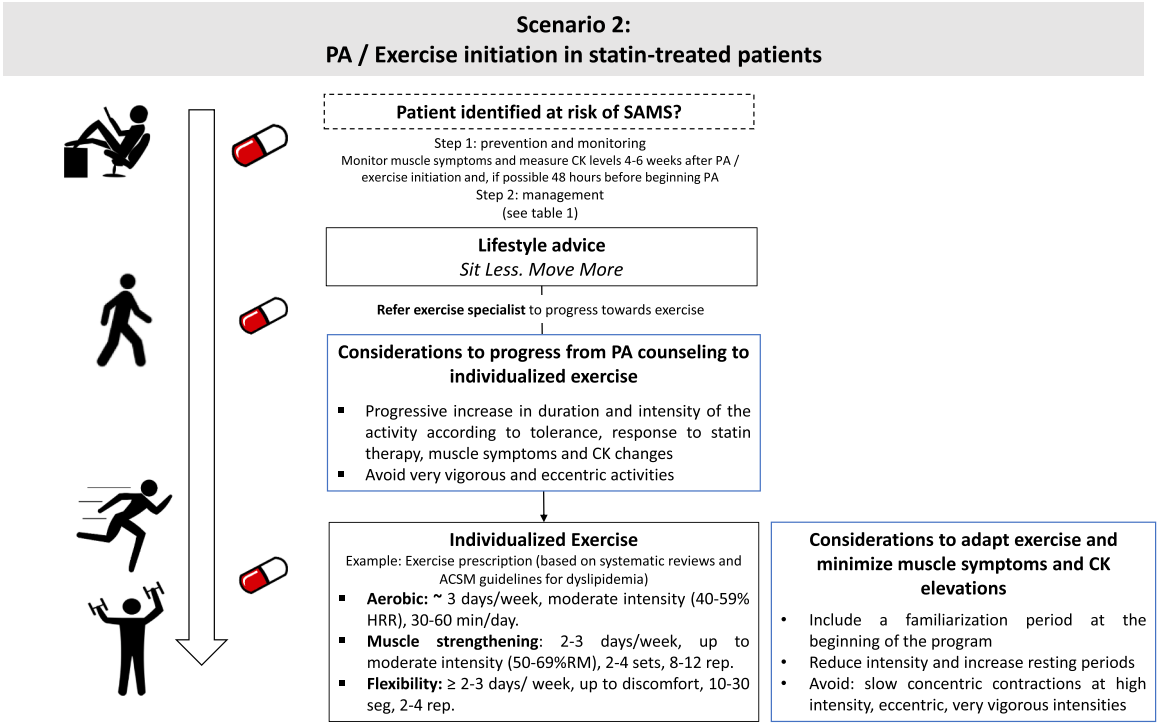

Fig. 2. Scenario 2: PA/exercise initiation in statin-treated patients.

intensity of training and competition. It must be noted that the ILEP built their recommendations based either on previously sedentary and inactive individuals, studies assessing the acute (not chronic) effects of PA, or professional athletes [16]. To our knowledge, the effects of initiating statin therapy in physically active individuals (besides athletes) remain to be investigated. Clinicians should differentiate groups of patients along the spectrum of physically active individuals (see Fig. 3) in order to provide more accurate recommendations on how to initiate statin therapy. For those physically active patients on the most conservative end of the PA spectrum (i.e. performing 150 min/week of aerobic PA and 2 days/week of muscle-strengthening activities at moderate intensity), less risk of SAMS development when starting statin therapy might exist [29,30]. In these cases, monitoring muscle symptoms and measuring initial CK levels (before statin initiation) and 4–6 weeks after statin initiation is recommended [16]; moreover, during the first weeks of treatment, assessing CK levels 48–72 h after the activity can help make decisions. In addition, physicians should consider referring to exercise specialists to include modifications in exercise dose (reducing duration and intensity, increasing resting periods, avoiding hypertrophy and eccentric training) when statin therapy is started. If statins and exercise are well tolerated, exercise dose could be gradually increased (see Fig. 3).

5. Statin therapy initiation in athletes and very active individuals performing SAMS-risky activities (scenario 4)

Physically active patients on to the higher end of the PA spectrum (i.e. professional athletes participating in competitive sports) or those performing activities that might increase risk of SAMS (extensive or high-intensity exercise, hypertrophy training, or PA with a high eccentric component), make up a different scenario that requires special considerations (Fig. 4). Athletes have increased CK levels compared to the general population [43,44], with up to twice the CK levels of physically active non-athletes and up to 6 times the CK levels of inactive individuals [44]. This is probably because of the greater muscle mass and the daily vigorous training performed, although considerable interindividual variability exits [45]. Although elevated CK is not the only factor indicative of SAMS [46], this factor must of special relevance in this scenario. Indeed, previous studies conducted in different populations of athletes have evidenced greater incidence of SAMS [47] and difficulties to tolerate statin therapy in this specific population [48]. CK levels in athletes might also vary depending on the exercise modality and competition demands [44], stressing the special relevance of individualization in this scenario. Although CK reference values for each sport are not described [16], certain exercise modalities have been suggested as potentially risky for SAMS development and should be carefully considered before statin initiation. In extensive aerobic exercise modalities (such as marathon or triathlon), previous studies in statin treated individuals evidenced greater increase in CK levels [49] and a case of rhabdomyolysis [50] has been reported after a marathon. High-intensity exercise (i.e. activities over 64% of the maximal oxygen uptake, over 77% of the maximal heart rate, or resulting in a rating of perceived exertion of >14 on the Borg 6–20 scale [51]) might also increase the risk of SAMS [16]. These exercise intensities are easily surpassed on everyday practice for most athletes at any competitive level and for non-athletes who undertake high-intensity activities such as cross-fit or similar. Individuals who perform hypertrophy training are also at risk of muscular damage, pain, and increased CK levels since this training modality is aimed at producing high muscular strain and damage. The ILEP and the EAS/ ESC recognize the possibility of muscle symptoms and CK elevation in this context [16]. Activities with a high eccentric component (i.e. downhill running) are also considered a potential cause of muscle damage and CK increases [16]. For patients included in this scenario, in addition to SAMS, a decrease in physical fitness as a result of statin initiation might be a concern. Although there are still inconsistent results on this issue, recent evidence supports that statins does not adversely affect the exercise capacity or performance [28,52,53]. Indeed, some studies suggested that lower muscle performance seen with statins could be related to pre-existing low PA levels (leading to hypercholesterolemia and need for statins), rather than

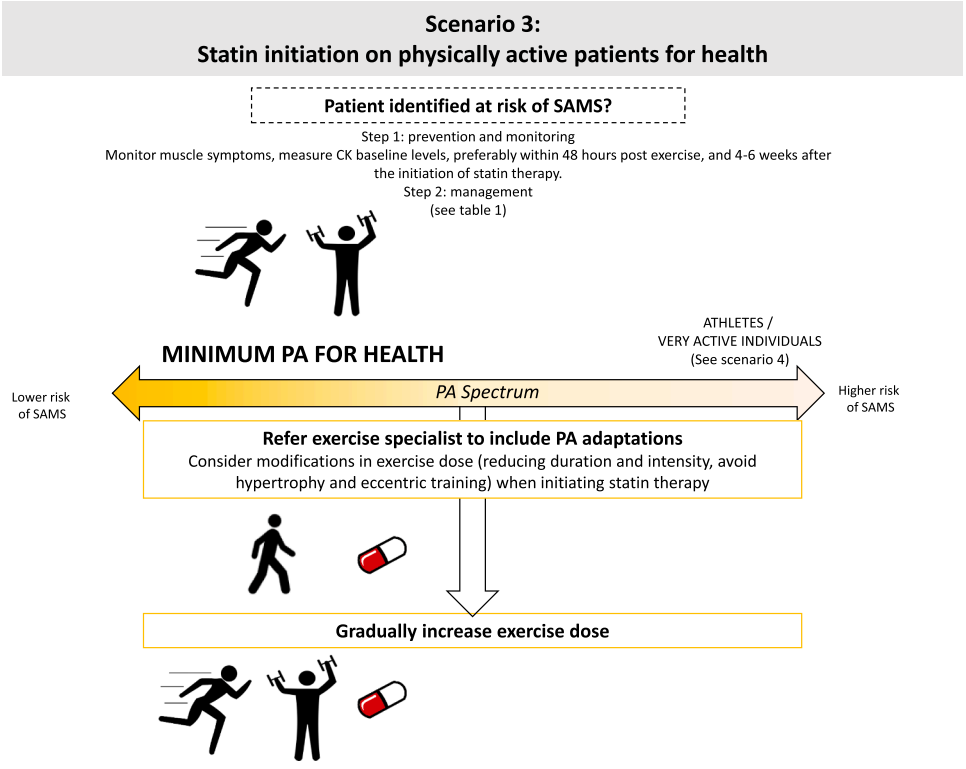

Fig. 3. Scenario 3: Statin therapy initiation in physically active patients.

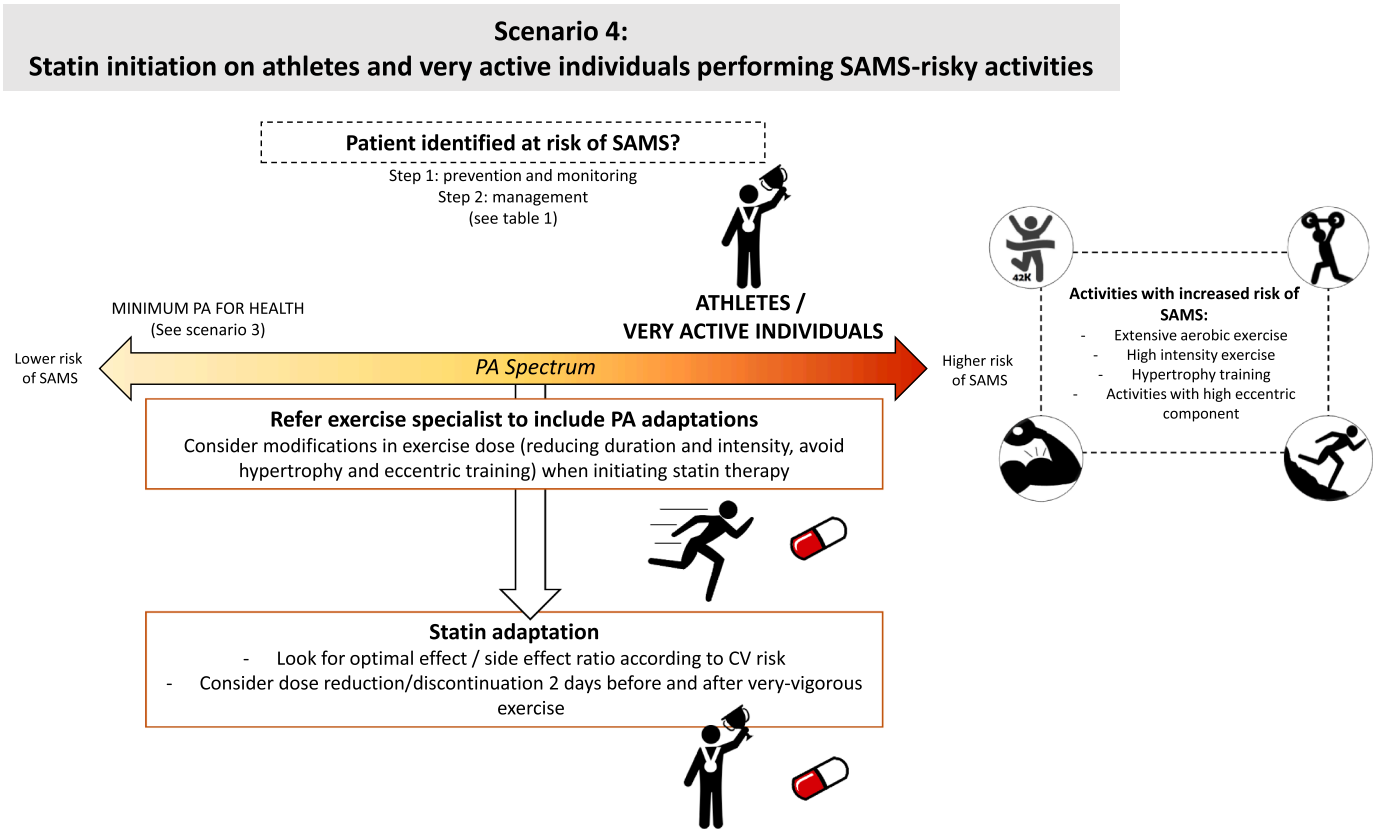

Fig. 4. Scenario 4: Statin therapy initiation in athletes and very active individuals performing SAMS-risky activities.

statins themselves [54].

6. Specific considerations for SAMS prevention and management in active patients

As a general rule, physically active patients should not be discouraged from their regular activity, although statin therapy must be prioritized to optimize the CV risk-benefit ratio [16]. For instance, in situations in which CV risk is particularly high (e.g. patients with familial hypercholesterolemia), priority should be given to statin treatment over exercise and efforts to prevent SAMS will be particularly relevant [16]. Regarding exercise, we tentatively propose modifying the PA dose (e.g., reducing the duration and intensity) and avoiding hypertrophy and eccentric training when starting statin therapy as a reasonable preventive approach, particularly for non-professional athletes and those undertaking exercise for leisure, although this deserves further research.

Frequently, the contribution of statin therapy to increased CK levels may be difficult to distinguish from exercise-related CK elevations. Therefore, in order to prevent SAMS, measurements of CK levels should be performed before statin initiation, preferably within 48 h post exercise, and 4–6 weeks after the initiation of statin therapy [16]. Preventive approaches related to statins might include a reduction in statin dose (or even temporary discontinuation) for at least 2 days before and at least 2 days after scheduled SAMS-risky activities, an alternate day or twice-weekly dosing regimen, as well as non-statin lipid-lowering drugs (in monotherapy or in combination with a statin) according to individual CV risk [16]. Long-term discontinuation of statin treatment in a high-risk patient with moderate elevation of CK is not recommended due to increased risk of CV events [16]. Occasionally, using a hydrophilic statin, such as pravastatin or rosuvastatin, the latter occasionally just a few days per week, or using pitavastatin, daily or a few days per week, have also been used successfully in some patients and athletes [55].

If muscle symptoms present with CK increases $\leq$ 4 times of the upper limit of normal (ULN) or if exercise contributes significantly to CK elevation, reduction or modification of exercise are recommended in the case of a high or very high-risk patient [16]. If exercise is excluded as the main cause of the CK elevation, and CK increases between 4 and 10 times of the ULN, statin should be discontinued for at least 2–3 weeks and re-challenge should be considered. Reduction and / or modification of exercise could be also considered in these cases. If symptomatic, significant CK elevations reappear with at least two different statins or if CK increases to more than 10 times the ULN, discontinuation of statin treatment and exercise is recommended.

7. Potential for non-statin lipid lowering medication

When the re-challenge of the statin (at lower dose, intermittent dosing or switching to a different statin) is not effective or refused by the patient, other alternatives can be explored. Individual studies and meta-analyses have suggested some potential of Coenzyme Q 10 therapy to reduce SAMS [56,57] (thus allowing patients to continue statins) and can also increase performance in athletes on statins [58]. However, two recent meta-analysis questioned these benefits [59,60] and further research is required to establish firm recommendations. A more consistent agreement exist on the use of other non-statin lipid lowering agents, such as ezetimibe, PCSK9 inhibitors, or bempedoic acid when statins are not tolerated [61]. Ezetimibe acts reducing the absorption of cholesterol from the intestine and have shown a very low risk of adverse muscle effects, although physicians should adequately inform to patients that this drug is not a statin [62]. PCSK9 inhibitors, (alirocumab and evolocumab), which reduce the levels of circulating LDL-C by increasing the expression of LDL-C receptors on hepatocytes, have also shown a very safe muscular profile [62]. Lastly, bempedoic acid, a recent drug that significantly reduce LDL-C by inhibiting the pathway of cholesterol biosynthesis, seems to be very well tolerated and to have a very low

incidence of muscle-related adverse events [62,63].

8. Conclusions

In conclusion, although compelling evidence highlights the key role of statins and the benefits of PA for CV protection, the concurrent prescription of both therapies still requires extensive research. We propose a practical approach based on the four most prevalent scenarios under which decisions might require different considerations. The benefits of statin therapy seem to outweigh the risks, and improving the provider-patient communication could prevent the nocebo effect that greatly influences most cases of SAMS. Regarding PA, the history of practice along with its frequency, intensity, time and type differently affect the appearance of SAMS. Clinicians should balance the benefits and risks of concurrently prescribing statin therapy and PA to provide the best evidence-based prescription in each case. We hope that our work will contribute to make better decisions and will spur further research to optimize the CVD protection of patients at moderate to high CVD risk.

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CRediT authorship contribution statement

Blanca Gavilán-Carrera: Conceptualization, Methodology, Writing – original draft, Visualization. **Alberto Soriano-Maldonado:** Conceptualization, Methodology, Writing – original draft, Visualization, Supervision, Project administration. **Juan Diego Mediavilla-García:** Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Carl J Lavie:** Conceptualization, Writing – review & editing, Visualization. **José Antonio Vargas-Hitos:** Conceptualization, Methodology, Writing – original draft, Visualization, Project administration.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data Availability

No data was used for the research described in the article.

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