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Identification and management of patients with statin-associated symptoms in clinical practice: A clinician survey

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ABSTRACT

Background and aims: Discontinuation of statin therapy by patients with hypercholesterolemia because of the onset of side-effects (statin-associated symptoms [SAS]) increases the risk of cardiovascular morbidity and mortality. We aimed to understand how patients with SAS, particularly those with statin-associated muscle symptoms (SAMS), are identified and managed in the outpatient setting.

MethodsA web-based survey involving 60 clinicians in each of 12 countries and 90 clinicians in the US was conducted. Clinicians answered questions about the diagnostic criteria, estimated incidence of SAS, and choice of treatment for patients with SAS.

ResultsOverall, 810 clinicians (78% cardiologists) completed the survey. An average of 72% of patients with potential SAS were reported to present with muscle-related symptoms (range across countries [RAC] 50–87%) that could be SAMS. Clinicians took a range of steps to confirm SAMS in these patients, including discontinuation of statin (average 59%; RAC 48–67%); re-challenge with ≥2 statins (average 74%; RAC 60–85%); modification of statin regimen (average 76%; RAC 65–85%); or a combination of these steps. Overall, 6% of patients with hypercholesterolemia were estimated to eventually have SAS (RAC 2–12%). In patients with SAS, on average 52% continued to receive a low-dose statin, usually with other lipid-lowering therapies (LLT). Of the remaining 49%, 38% received alternative LLT only; 11% did not receive any LLT.

ConclusionThere is some consistency and stringency in clinical practice for identifying patients with SAS; however, a structured work-up for identification, followed by a defined therapeutic algorithm, may improve their management.

1. Introduction

High plasma levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are important and modifiable risk factors for cardiovascular disease (CVD) [11]. Statins are the first choice of pharmacological treatment to reduce LDL-C [16]. The beneficial effects of statins on CVD outcomes have been shown in a large number of clinical trials, both in patients who have already experienced a CVD event (secondary prevention) and in those who are free of CVD at randomization (primary prevention) [16,19].

Statins are well tolerated by the majority of patients and serious adverse events are reported infrequently in clinical trials [1]. However, some patients do experience side-effects (statin-associated symptoms [SAS]), a minority of whom will require a decreased dose or may discontinue statin therapy altogether; these patients are often referred to as being “intolerant to statins”. The most frequently reported SAS are muscle-related symptoms (e.g., muscle pain or weakness), referred to as statin-associated muscle symptoms (SAMS) in recently published clinical guidelines [15];

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however, patients may also present with hepatic, gastrointestinal, or central nervous system (CNS) side-effects [4,8,12,15].

Estimates of the prevalence of SAS vary widely depending on the source of data and the definition used to register the symptoms. Some observational studies have reported that up to 20% of patients treated with statins had experienced SAS, in sharp contrast to the 3–6% reported in randomized controlled trials (RCTs) [5,20]. More importantly, prevalence of SAMS has been similar in placebo and statin-treated groups in all major RCTs [10], attesting to the concept that psychological aspects contribute significantly to this phenomenon. Notwithstanding its exact pathophysiology, persistent SAS constitutes a serious clinical entity in daily practice, because patients who discontinue statin therapy are at increased risk of cardiovascular morbidity and mortality [7,13,20]. Discontinuation of statin therapy for any reason after acute myocardial infarction led to a 4–7 fold increase in cumulative cardiac mortality [7].

Two clinical guidelines have been developed recently to help clinicians with the evaluation and treatment of patients presenting with SAMS [12,15]. The National Lipid Association guidelines focus on the identification of patients with SAMS [12], and the European Atherosclerosis Society (EAS) Consensus Panel statement provides guidance on their management [15].

We investigated how patients with a range of signs or symptoms associated with intolerance to statin therapy (i.e., SAS) are currently identified and managed in clinical practice by conducting a web-based survey of clinicians across 13 countries.

2. Methods

This cross-sectional web-based survey among clinicians specializing in the treatment of patients with hypercholesterolemia was conducted across Australia, Brazil, Canada, France, Germany, Italy, Japan, the Netherlands, Poland, Spain, Sweden, the UK, and the USA, between January and February 2014.

2.1. Questionnaire development and administration

The survey questionnaire was developed in close collaboration with clinicians, using a three step iterative process [14]. Notably, at the time this survey was conducted, the term statin-associated muscle symptoms had not been used in clinical guidelines; participating clinicians were therefore asked about signs and symptoms associated with “intolerance to statins” or “patients with statin intolerance”.

The survey was implemented in two phases: a pilot phase to validate and test the clarity and ease of use, followed by the main phase (Fig. 1). Ethics approval was granted by the Human Research Ethics Committee of the University of Technology, Sydney; all participants provided informed consent before taking part in the survey.

The final questionnaire comprised 49 questions and took approximately 45 min to complete. Clinicians were requested to answer the questionnaire based on recollection of their experience in routine clinical practice. A summary of the questionnaire is provided in Supplementary Table 1. The survey was translated into the clinicians' native languages.

A screening tool in the questionnaire assessed eligibility of clinicians to participate in the survey. Eligible clinicians had to be specialists (cardiologists, lipidologists, endocrinologists, or internists) or general/family physicians (GPs) who had practiced for at least 2 years since completing their specialist training. In addition, specialists had to have treated at least 75 patients for hypercholesterolemia with pharmacological therapies in the previous 12 months; GPs had to have treated at least 50 patients; at least five patients with statin intolerance should have been treated in the previous 12 months. Clinicians who met the screening criteria proceeded directly to the full questionnaire; responses were anonymized, translated into English where necessary, and securely transferred to the research team (originals and translations) for electronic storage with restricted access. Data from incomplete surveys were not used in the final analyses.

Target specialists were cardiologists and endocrinologists; quotas were implemented with the aim of recruiting approximately 75% cardiologists and 25% endocrinologists/lipidologists in each country. In Japan, lipidologists/internal medicine clinicians replaced endocrinologists because of local treatment practice. Given the potential for regional variation in practice and the large number of clinicians to be recruited, regional quotas were also implemented based on the distribution of the population in each country. Recruitment continued until the target number of participants was reached: 60 per country (40 specialists, 20 GPs; 60 specialists and 30 GPs in the USA). The bigger sample size in the USA ($n = 90$) was based on the larger population compared with other scope countries.

Recruitment, survey translation, and data collection were performed by an agency specializing in healthcare fieldwork, following the guidelines of the British Healthcare Business Intelligence Association, Pharmaceutical Marketing Research Group, European Pharmaceutical Market Research Association, and the Council of American Survey Research Organizations. All participants were remunerated for their time at the nominal fair market rate prevalent in their country.

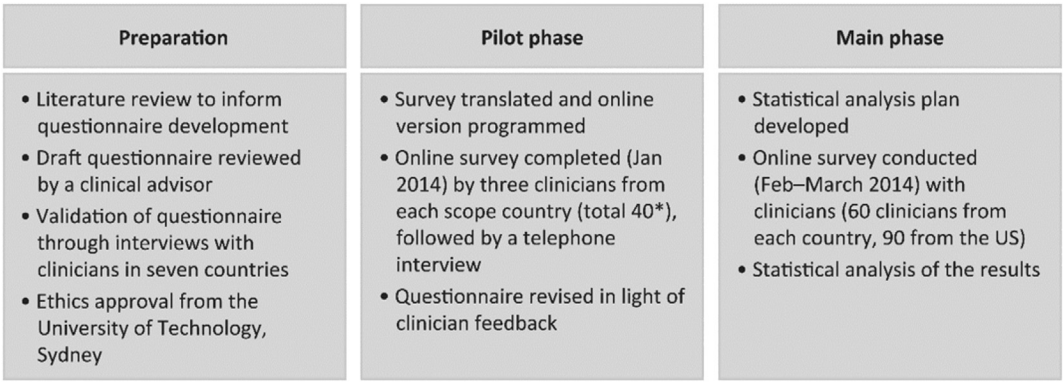

Fig. 1. Study overview. *Four clinicians were recruited for the pilot survey in Japan (one cardiologist, one endocrinologist, one internist, one GP); a total of 40 clinicians were involved in the pilot survey.

2.2. Statistical analysis

All data were analyzed separately for each country according to a pre-specified statistical analysis plan. The study was not powered to make comparisons between countries.

All analyses were carried out using the statistical software package SAS (version 9.2 or later) and were independently verified by a statistician.

3. Results

3.1. Demographics of study participants

A total of 2653 clinicians were screened for potential participation in the survey; 1525 (57.5%) met the eligibility criteria, of whom 810 (53.1%) participants completed the survey. The planned sample sizes were achieved in all countries except in Australia where the 60 respondents comprised 39 specialists and 21 GPs. Across countries, an average of 77% of specialists were cardiologists. In countries other than Japan, 19% of the specialists were endocrinologists and 4% were lipidologists; in Japan, 5% of the specialists were lipidologists and 20% were internal medicine specialists.

3.2. Identification of patients with SAS

3.2.1. Signs and symptoms associated with statins

Respondents across all countries reported that muscle-related symptoms were the most common symptom among patients with SAS (range of values across countries 50–87%) (Fig. 2). Notably, no further definition of muscle-related symptoms was provided in the questionnaire to avoid any bias in their responses. Based on clinicians' responses, an average of 30% of patients across countries were reported to have elevated creatine kinase (CK) levels but no muscle-related symptoms, and 28% showed persistent elevation in transaminases. Only 4% of patients were reported to present with CNS effects and an average of 18% with other symptoms (e.g., gastric symptoms, alopecia).

3.2.2. Minimum criteria used in clinical practice to establish SAMS in patients with muscle-related symptoms

Across countries, respondents generally used similar criteria to establish whether a patient presenting with muscle-related symptoms had SAMS. Four main criteria were widely used as a minimum: discontinuation of the statin, rechallenge with the same statin, trying at least two different statins, and rechecking that elevated CK levels decreased after modifying or stopping statin treatment.

An average of 74% clinicians (range 60–85% across countries) reported that they would rechallenge patients with the same statin therapy to determine whether muscle-related symptoms reappear (Fig. 3a). Those who did not report rechallenge would try either discontinuing the statin (without rechallenge) or lowering the dose; a small number of clinicians selected none of these options (one GP in the UK; three GPs in France).

An average of 38% clinicians (range 32–46% across countries) reported using a combination of discontinuation, rechallenge, and lowering the statin dose before classifying a patient as having SAMS. This combination of actions was the most commonly reported in all countries except Poland, where rechallenge with statin therapy alone was the most commonly used criterion.

The clinicians also reported trying a number of modifications to the statin regimen before considering a patient to have SAMS; the most commonly reported modification was a combination of trying at least one statin at a lower dose, at least one statin at an intermittent dose, and at least two additional statins. When asked specifically about the number of statins they would try, an average of 76% clinicians (range 65–85% across countries) reported that they would try at least two statins before considering a patient with muscle-related symptoms to have SAMS (Fig. 3b).

An average of 82% of clinicians (range 73%–88% across countries) also reported rechecking serum CK levels after stopping or modifying statin therapy in patients with elevated serum CK levels.

3.2.3. Estimates of the prevalence of statin-associated symptoms

Clinicians were asked to estimate how many of their patients with hypercholesterolemia are newly prescribed a statin in a year, and the proportion that present with signs or symptoms that could be associated with intolerance to statin therapy (i.e., SAS). In a separate question, clinicians were also asked to estimate the percentage of their patients that are newly prescribed statins who present with symptoms of possible 'statin intolerance' and are later confirmed to be unable to tolerate statins at a dose below the label recommendation. Based on their responses, we estimated the overall rate of possible statin intolerance and the average number of patients confirmed as having intolerance. An average of 25% of patients with hypercholesterolemia who are treated with statins

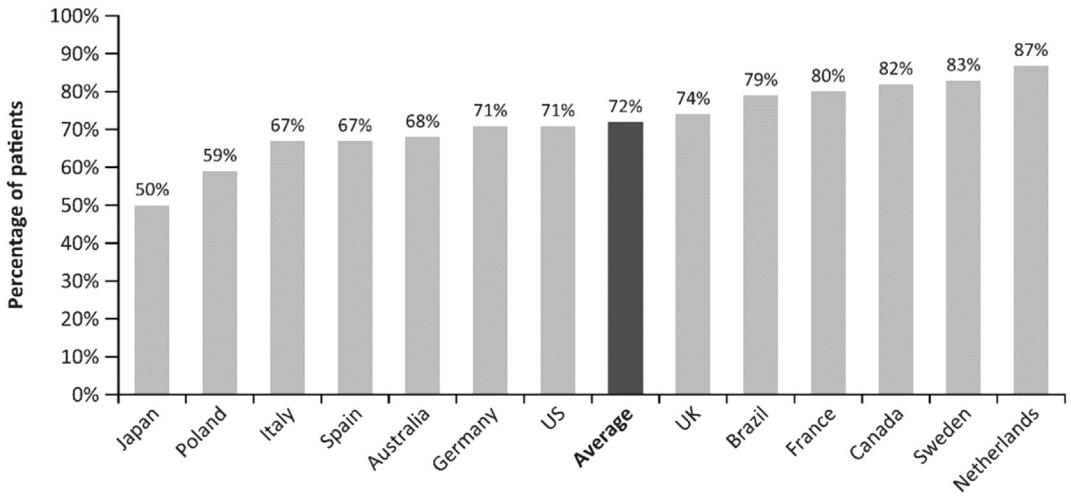

Fig. 2. Proportion of patients newly prescribed statins reported to present with potential statin-associated muscle symptoms.

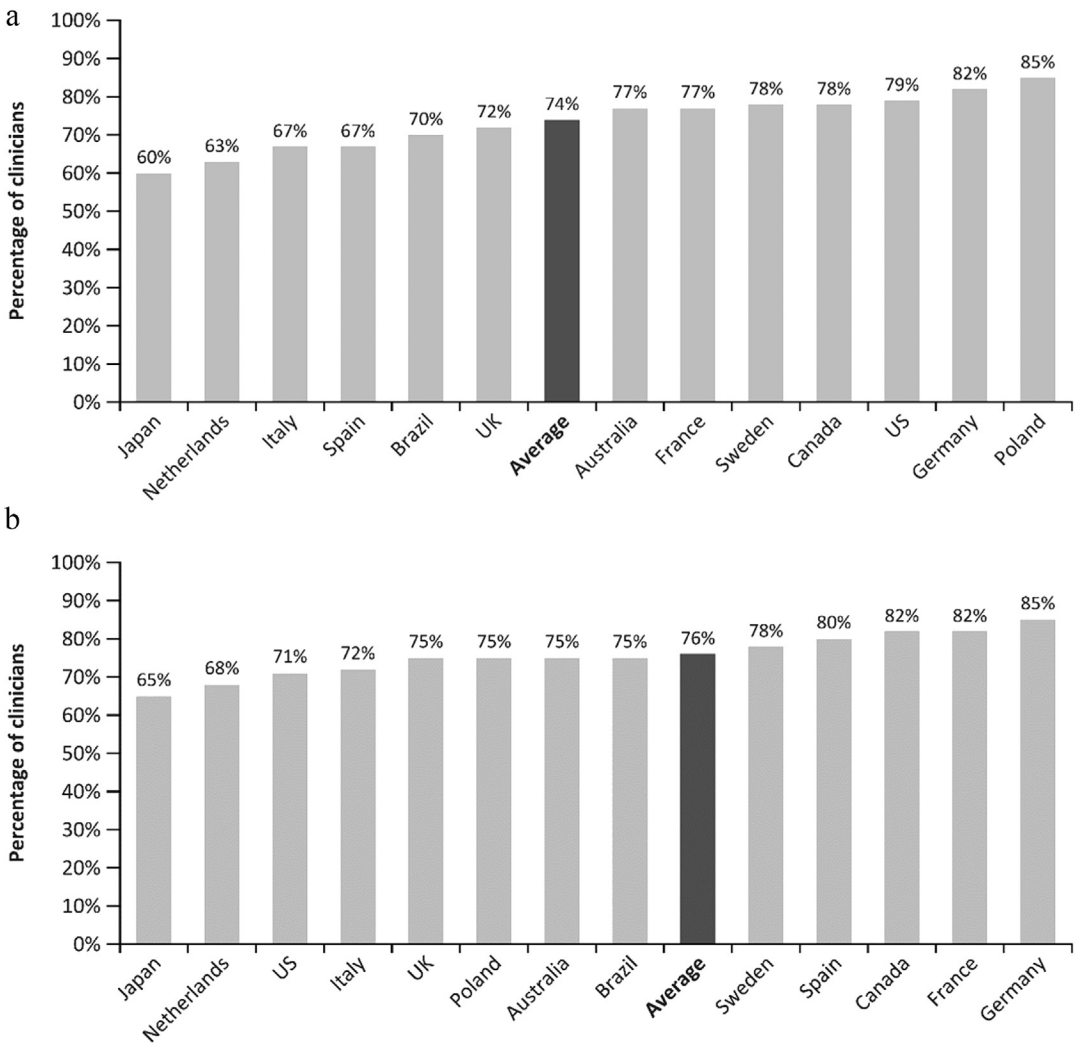

Fig. 3. a. Proportion of clinicians who rechallenge as a minimum requirement before considering a patient to have SAMS. b. Proportion of clinicians who try at least two statins before considering a patient with muscle-related symptoms to have SAMS.

have signs and symptoms that may indicate intolerance (range 11–48% across countries). Of these patients with signs and symptoms that may indicate intolerance, an average of 22% (range 11–36% across countries) are unable to tolerate statins at the recommended therapeutic dose. Therefore, it is estimated that an average of 6% of patients (22% of the 25% of patients presenting with symptoms) with hypercholesterolemia who are treated with statins will be confirmed as being unable to tolerate statins at the recommended therapeutic dose (range 2–12% across countries, Fig. 4). This percentage was similar for specialists (1–12%) and GPs (2–12%). Of the estimated 6% of patients unable to tolerate statins, an average of 64% of patients were estimated to have SAMS.

3.3. Treatment of patients with statin-associated symptoms

3.3.1. Continued treatment with statins

Clinicians in all countries except Japan reported that approximately 50% of high-risk patients (e.g., those with a previous CVD event, with comorbidities, or heterozygous familial hypercholesterolemia) with SAS continue to receive statins at a dose below that recommended by the regulatory label. Japanese clinicians reported that 71% of patients with SAS do not receive any statin treatment.

Across countries, clinicians reported that more than half of patients receiving low-dose statins also received another lipid-lowering therapy. The majority of high-risk patients who were unable to tolerate statins at an appropriate dose received a lipid-lowering therapy. A small proportion of these patients (5–17%) did not receive any statins or other non-statin lipid-lowering therapies. Fig. 5 summarizes the treatment pathway inferred from clinicians' responses across countries for patients who were unable to tolerate statins at the label-recommended dose (because of SAS).

3.3.2. Use of non-statin lipid-lowering therapies

Clinicians were asked which non-statin therapies they most frequently used as monotherapy (i.e., without a concomitant statin) or in combination with low-dose statins for patients with SAS. Across all countries, with the exception of Poland and the USA, most clinicians (average 72%) reported that they used ezetimibe most frequently, as monotherapy or in combination with a low-dose statin (average 75% clinicians). Fewer clinicians in Poland (48%) and the US (44%) reported using ezetimibe monotherapy.

Many respondents also considered a range of other treatments, including fibrates, fish oil, cholestyramine, and niacin/nicotinic acid to be among the top-three most commonly used lipid-lowering therapies, although these were rarely their first choice.

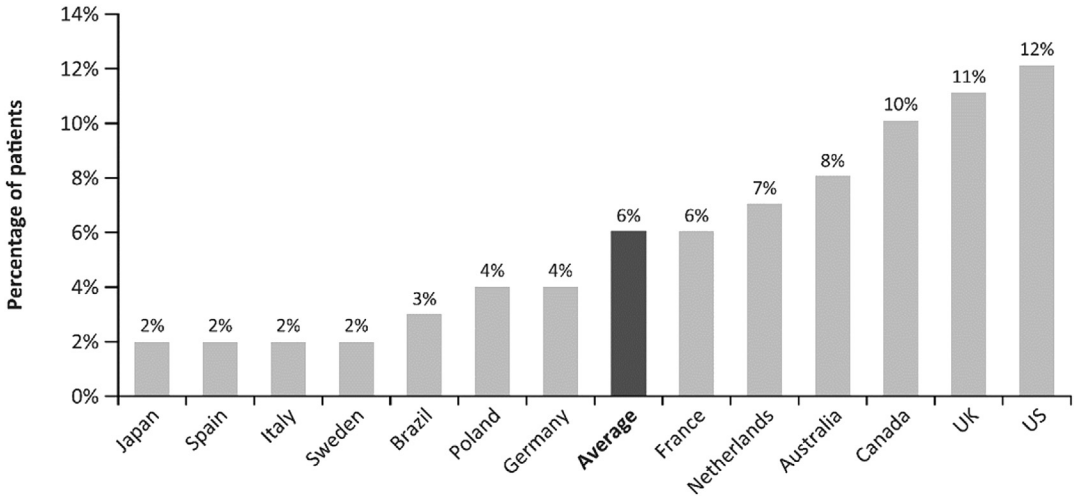

Fig. 4. Estimated proportion of patients confirmed to have intolerable statin-associated symptoms.

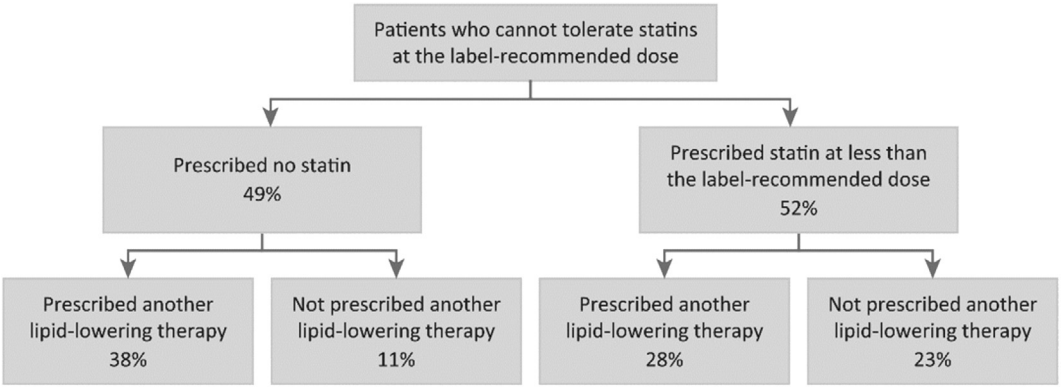

Fig. 5. Treatment strategies for patients who cannot tolerate statins at the label-recommended dose. Values are the average proportions of patients across all countries (percentages may not total 100% because of rounding).

3.3.3. Treatment outcomes with non-statin therapies

The clinicians were asked to estimate the proportion of their patients with SAS who reach lipid targets set by current clinical guidelines and the proportion they consider to be satisfactorily treated with lipid-lowering therapy. Across countries, 21–41% of patients were estimated to reach lipid targets, and 26–43% were perceived to be satisfactorily treated in the opinion of the clinician. These estimated proportions were similar in all countries except the Netherlands, where clinicians estimated that 17–32% of patients reach lipid targets but 36–57% were treated satisfactorily.

4. Discussion

To our knowledge this is the first study to elicit detailed responses from clinicians regarding their individual approach to identifying and treating patients with SAS ("intolerance to statin therapy" in the questionnaire) in routine clinical practice. Clinical guidelines available at the time of this study did not provide explicit criteria to identify and manage patients with SAS. However, clinical guidelines published after this survey was completed have provided guidance for the evaluation and treatment of patients presenting with SAMS [12,15]. Overall, the clinicians' responses in our survey have established that they are aware of the existence of SAMS as well as other SAS; however, in the absence of clear clinical guidance, they developed individual practices to identify patients with SAMS. The eligibility criteria for participation in this web-based survey were well-defined and strictly followed to ensure that survey respondents were experienced in managing patients with SAS and as such grossly reflect the opinion of those who treat a large number of such patients.

The survey results did not reveal a consensus about any single set of criteria used to identify SAS in clinical practice; however, it identified some clear trends. Clinicians reported that patients with potential SAS most frequently presented with muscle-related symptoms (SAMS); although the proportion ranged between 50% and 87% across countries, these numbers are consistent with those reported in literature [8]. It is of note that the overall response with regard to the definition (symptoms upon two different statins) and treatment (lower dose, different statin in combination with ezetimibe) are in accordance with the recently published guidelines [2,15]. The latter set of guidelines, recently developed by an International Lipid Expert Panel, suggest a unified definition of statin intolerance [2]; however, the adoption of consistent definitions and clinical practice is likely to take time.

Clinicians across all countries reported taking a range of steps to establish SAMS, such as discontinuation, rechallenge, and lowering the statin dose. Importantly, the survey also revealed that the different steps to establish SAMS are generally not taken alone but in combination. Broadly, there was consensus that rechallenge in combination with trying at least two statins was important;

however, the details varied across countries. Clinicians across all countries also reported that in the small proportion of patients with elevated serum CK levels, they took the additional step of rechecking CK levels after modifying or stopping statin treatment to confirm SAMS. The majority of survey respondents used more strict criteria to confirm SAMS in patients at high risk of CVD events, suggesting they try harder to manage these patients with existing treatment options. Notably, the EAS Consensus Panel's recent guidance recommends rechallenge and trying at least three statins to identify patients with SAMS; treatment with the maximum tolerated dose of statin in combination with non-statin therapies is recommended to attain LDL-C targets in these patients [15]. Similarly, the National Lipid Association's (NLA) consensus guidelines also recommend using at least two statins in patients with SAMS [12]. In our study, the majority of clinicians reported rechallenging or using at least two statins before determining that a patient has SAMS. These findings suggest that the EAS consensus statement and NLA consensus guidelines published after the survey was conducted are consistent with the clinical practice reported in this study. A recent study highlighted that individual patients with reported SAS may report these symptoms even when prescribed a placebo in a blinded trial (the 'nocebo effect'); however, they may be amenable to restarting statin therapy when presented with evidence that their symptoms are not due to statins [6]. This blinded cross-over trial approach may provide more convincing evidence for establishing causality at the level of individual patients and establish the extent to which the nocebo effect confounds current clinical practice. In a larger trial, 120 patients with simvastatin-associated myalgia were assigned in a double-blind, crossover trial to study the effect of CoQ10. In the run-in phase of the study, 35.8% of patients experienced myalgia on simvastatin and not on placebo, while 17.5% of patients had no symptoms on simvastatin or placebo. However, 29.2% experienced pain on placebo but not on simvastatin, and 17.5% experienced pain on both the statin and placebo during the confirmation phase [17].

Although the study was not statistically powered for epidemiology analysis or interpretation, our findings suggest that, based on clinicians' responses, an average of 6% of patients with hypercholesterolemia who are treated with statins have SAS that renders them unable to tolerate statins at the recommended dose (which includes patients who discontinue statin or receive a reduced dose) (range 2–12% across countries). This proportion is consistent with the range of 5–10% reported in the literature [5,9,20]. Overall, it suggests that in real-world practice, clinicians recognize the importance of SAS in patients with hypercholesterolemia and attempt to mitigate their high risk of a CVD event to the extent possible with available strategies.

Importantly, the overall consensus amongst clinicians was that there are limited treatment strategies for patients with SAS. Across all the countries except Japan, clinicians' responses demonstrate that they continue to treat patients with a low dose of statin whenever tolerated. Nevertheless, a proportion (approximately 11%) of patients with SAS receive no treatment at all. Alternative lipid-lowering therapy (i.e., without concomitant low-dose statin) is used to treat a substantial proportion of patients (average 38%); however, fewer than half of patients treated with non-statin therapies were reported to reach lipid targets or to be treated satisfactorily. This suggests that effective treatment options for patients with SAS are limited or, alternatively, that clinicians are not fully exploring the potential of currently available strategies for managing these patients.

Clinician surveys conducted with high methodological rigor are an invaluable tool to gather reliable real-world data for assessing various aspects of drug use, including efficacy and safety under real-life conditions [18]. A few potential sources of bias and limitations were identified in our web-based survey. (1) The survey included only clinicians who manage large number of patients with hypercholesterolemia with pharmacological therapies. The responses from those who participated may therefore not be generalizable to all clinicians, particularly those who treat fewer patients. (2) More patients with SAS are likely to be referred to specialists; therefore estimates of symptom prevalence provided by these specialists are likely to be skewed and unlikely to represent the entire population taking statins. (3) To avoid biases from differences in clinical practice, the study included specialists and GPs in a fixed ratio, and the selection was designed to be representative of the types of specialists involved in managing patients with SAS in real-world practice. However, we were unable to explore differences between specialists because of the small sample sizes achieved in individual categories across countries. (4) Clinicians who had registered with the agency as willing to participate in online research may not be representative of all clinicians who treat patients with SAS in each country. (5) The study has relied on clinicians' responses to the questionnaire, not the decisions they actually make in clinical practice. Some clinicians may have interpreted certain questions incorrectly. (6) Although this was an anonymous web-based survey, it is plausible that clinicians may be inclined to report what they should be doing in their practice rather than what they are actually doing.

In spite of these known limitations, our methodology was robust and incorporated several design features recommended in the literature to gather reliable and unbiased data [3]. It strictly followed the pre-specified statistical analysis plan, was conducted according to ethical guidelines, used a questionnaire validated through a pilot survey, and was designed to understand clinicians' practices at an aggregate level. This should reduce the potential bias resulting from clinicians feeling obliged to report treatment procedures based on what is recommended in clinical guidelines, rather than their actual clinical practice. Recruitment quotas and screening criteria were included to ensure that surveyed clinicians were representative of clinicians from different regions of the country who treat patients with hypercholesterolemia who experience SAS in real-life clinical practice.

Consequently, we consider the results of our study to provide novel and valuable insights into how patients with SAS are being identified and treated in current clinical practice.

5. Conclusion

Clinicians consider it imperative to try to continue statin therapy in patients with SAS and higher CVD risk by appropriate counseling and repeated discontinuation and rechallenge with various statin regimens [12,15]. Despite this approach, a minority of patients are unable to tolerate statins at therapeutic doses. Reliable identification of these patients with persistent and intolerable SAS may improve the management of those at risk of a CVD event and lead to better clinical outcomes. Evidence from this survey identifies some consistency and stringency in practice among clinicians when diagnosing SAS. Additional research and guidelines are likely to further encourage reliable identification and better management of patients with SAS.

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Ethics approval for this study was obtained from the Human

Research Ethics Committee of the University of Technology, Sydney.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.12.015.

Conflicts of interest

This survey was sponsored by Amgen Inc. and conducted by PRMA Consulting Ltd. S. Gandra and R. Dent are employees of Amgen Inc. and own stock/stock options. J. McKendrick and H. Wieffer are employees of PRMA Consulting Ltd, and do not have competing interests. R. S. Rosenson has served as a consultant for Amgen, Astra Zeneca, Eli Lilly, Genzyme, Novartis, Regeneron, and Sanofi, and has received honoraria from Kowa and royalties from UpToDate, Inc. E. S. G. Stroes is a consultant to and receives honoraria from Sanofi, Amgen, Torrent, Eli Lilly, Novartis, MSD, and Cerenis. G. K. Hovingh, P. Oh and A. L. Catapano have no competing interests to declare.

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