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Original Articles

The STatin Adverse Treatment Experience Survey: Experience of patients reporting side effects of statin therapy

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BACKGROUND: It is important to understand patients' experiences of statin-associated adverse effects to potentially identify those at risk for stopping treatment.

OBJECTIVE: The goal of the STatin Adverse Treatment Experience survey was to describe patients' experiences after reporting ≥1 recent statin-associated adverse event and identify opportunities to improve adherence and outcomes.

METHODS: The survey was developed in 3 stages: qualitative item development, pilot evaluation of initial item performance, and quantitative evaluation using a large commercial sample. Respondents with self-reported high cholesterol who had taken a statin in the past 2 years and experienced ≥1 statin-associated symptom in the past 6 months were included (N = 1500).

RESULTS: Mean age was 58 years, 40.3% were men, and 43.2% had tried ≥2 statins. Many had clinical comorbidities associated with increased risk for cardiovascular disease (atherosclerotic cardiovascular disease, 22.5%; diabetes, 25.8%; hypertension, 56.0%). The most important patient-reported reasons for continuing current statin therapy (n = 1168; 77.9%) were avoiding a heart attack or stroke, lowering cholesterol, and doctor recommendation. Being bothered by and not being able to tolerate side effects were the main reasons respondents discontinued statins (n = 332; 22.1%). Respondents who discontinued statins reported significantly higher mean Symptom Severity (10.6 vs 8.7, $P < .001$) and Impact Severity scores (11.8 vs 9.8, $P < .001$) compared with those who continued.

CONCLUSION: The STatin Adverse Treatment Experience survey highlights the importance of patients' adverse experiences with statins and how symptom and impact scores affect decisions to continue or discontinue therapy. These data provide a foundation to increase providers' awareness of statin tolerability from the patient's perspective and encourage benefit-risk discussions.

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Introduction

Hypercholesterolemia is one of the most prevalent modifiable risk factors for cardiovascular disease, and statins are recommended as first-line pharmacologic therapy to reduce the risk of heart attack and stroke in most patients with elevated low-density lipoprotein cholesterol (LDL-C) levels and in most high-risk patients with atherosclerotic cardiovascular disease (ASCVD).[1–5] The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline recommended expanding the use of statin therapy in primary prevention to include more older adults and at-risk patients with elevated LDL-C, thereby substantially increasing the number of U.S. adults for whom statin therapy is recommended to 56 million individuals.[6] During 2012 to 2013, an estimated 28% of adults aged ≥ 40 years (39.2 million individuals) were taking statins.[7] Cholesterol-lowering medication use increases with age, with 43% of adults aged 60 to 74 years and 48% of adults aged ≥ 75 years receiving therapy during 2011 to 2012.[8]

The 2013 ACC/AHA guidelines also recommended moderate- to high-intensity statin doses for most patients. The updated 2018 ACC/AHA guideline now recommends high-intensity statin doses for many high-risk individuals.[1] Overwhelmingly, muscle-related symptoms are the most commonly reported side effects among statin-treated patients. In clinical practice and observational studies, approximately 10% to 29% of patients report statin-associated muscle symptoms[9–12]; these adverse experiences are a major factor for a change in statin therapy (ie, dose reduction or switch to a different agent), nonadherence, or discontinuation.[9,11,13–15] In the Understanding Statin Use in America and Gaps in Education (USAGE) survey, muscle-related side effects were more commonly reported in former statin users (60%) vs current statin users (25%).[9] In a real-world clinical setting involving 2 large primary care practices, this retrospective study showed that approximately 17% of patients experienced a statin-related event, and of those who discontinued statin therapy because of symptoms, most had a muscle-related event.[10] Finally, in a large medicare population (N = 105,329) receiving statin therapy after hospitalization for acute myocardial infarction, those who experienced statin intolerance had a 50% higher risk for recurrent myocardial infarction and a 51% higher risk of being hospitalized for recurrent cardiovascular events.[16]

In light of the prevalence of statin use and current guidelines recommending high-intensity statins to obtain the lowest possible LDL-C levels for many patients, based on evidence that lower LDL-C is associated with lower rates of major cardiovascular events,[1–3,17] it is important to understand the real-world impact of statin therapy from the perspective of the patients who are expected to take these medications, potentially for the rest of their lives. The National Lipid Association Statin Intolerance Panel has emphasized that statin intolerance is best understood from a patient-centric perspective.[18] To gain a better understanding of patients' experiences with statin therapy, we developed the STatin Adverse Treatment Experience (STATE) survey. The STATE survey engaged patients who had experienced ≥ 1 recent statin-associated adverse event to describe their experiences with treatment. The goal of the investigation was to develop a better understanding of patients' experiences with statin therapy to identify opportunities to improve adherence, medication management, clinical practice, and ultimately, outcomes. In addition, patient-reported symptom severity and impact on daily life were explored to characterize patients potentially at risk of stopping treatment.

Materials and methods

STATE survey development

Briefly, the STATE survey was developed by a team of expert clinicians and patient-reported outcome (PRO) measurement scientists in 3 stages. First, concept elicitation and qualitative item development was conducted in 2016 (N = 36). Second, a quantitative pilot validation of initial item performance was conducted in 2017 (N = 98). Third, the revised survey was used in a quantitative population-level evaluation using a large commercial sample in 2018 (N = 1500). The goal in selecting concepts for measurement and generating items for the STATE survey was to develop a content-relevant, low-burden, user-friendly survey that reflected the most important and relevant symptom and impact information obtained from patients with statin-related symptoms during the qualitative concept elicitation process. Item performance was then validated in the pilot study, and the final survey was fielded in a larger sample. All respondents provided informed consent before participating in any stage of the survey development; the privacy rights of all participants were always observed. Supplemental Appendix 1 provides the detailed methodology for the STATE survey development.

Stage 1: Concept elicitation and qualitative item development

In stage 1 of the STATE survey development, a qualitative study was conducted with the following 3 specific objectives:

1) To identify concepts relevant to patients' adverse experiences with statins,
2) to develop a draft PRO survey instrument based on content and language relevant to patients, and
3) to assess participant comprehension and thought processes used in formulating responses to the draft PRO survey.

In stage 1, a preliminary survey was developed after a literature review, interviews with opinion leaders, and qualitative interviews with patients (N = 36). Patients

with varying education and socioeconomic status were recruited from lipid clinics across the United States. The concept elicitation process involved patients describing their experience with statin therapy in their own words. Three waves of cognitive interviews were also conducted to assure proper comprehension of STATE survey items. The survey was drafted to cover the following 6 domains: demographics; clinical characteristics; health knowledge and beliefs; statin history; and statin symptom type, severity, and impact on activities of daily living. The preliminary survey items included preliminary versions of the Symptom Severity and Impact Severity Scales, which were constructed as scorable PRO measures and embedded into the overall survey.

Stage 2: Pilot validation of initial STATE survey item performance

The objective of the pilot evaluation of initial STATE survey was to collect initial quantitative data to evaluate the performance of the items contained in the STATE survey. There were 2 specific objectives:

1) To evaluate the item-level performance of the STATE survey, with particular focus on the psychometric performance of the embedded PROs for Symptom Severity and Impact Severity and
2) to identify variables within the STATE survey that differentiate groups of patients with and without statin-associated adverse events.

The information gathered was used to further refine the instrument and finalize the survey in preparation for a large population-based survey study. This pilot version of the STATE survey was web-based and taken via computer at the clinic sites across the United States with varying socioeconomic status populations. A total of 98 patients (49 with statin-related symptoms and 49 without) participated. After analyses of the pilot survey results, decisions to delete some items, revise select items, and add some new items were made (see Supplemental Appendix 1 for details).

The version of the STATE survey used in the pilot study included preliminary versions of a Symptom Severity Scale and an Impact Severity Scale. These PRO measures were based on qualitative interview data where patients reported a variety of symptoms, including muscle-related symptoms (aches, cramps, pain, soreness, fatigue, heaviness, stiffness, and weakness), joint/bone pain, joint stiffness, abdominal pain/cramps, memory problems, anxiety, depression, irritability, frustration, fatigue, exhaustion, lack of energy, and tiredness. While generating items for the Symptom Severity Scale, clinicians and researchers reviewed the more predominant patient-reported symptoms and considered their relation to statins. The initial data from the pilot study were used to evaluate the item-level performance and reduce the Symptom Severity PRO to the following items: muscle stiffness, muscle weakness, muscle pain, muscle aches, tiring easily, joint or bone pain, muscle cramps, and memory problems. Symptom items were answered using a 5-point response scale, with the score being the sum of the item responses (higher scores indicating greater symptomatology).

The Impact Severity Scale was designed to assess activities of daily living. Initial impacts reported by patients during the qualitative interviews included limitations on activities, needing to rest more, impacts on social relationships, having sleep affected, a variety of emotional impacts, increased use of health care, financial burden, and impacts to productivity (daily chores and overall performance). The concepts reported in the qualitative interviews were reflected in the pilot survey, and once data were analyzed, the Impact Severity PRO was reduced to the following items: reduced productivity and performance, reduced ability to be physically active or exercise, limited social activities, needing to rest more, increased need to interact with your doctor, and trouble getting good quality sleep. Impact items were initially answered using 0- to 10-point numeric rating scales, with the score being the mean of the item responses; however, scoring was subsequently changed to the use of 5-point verbal responses, similar to those used for the Symptom Severity measure (higher summary scores indicating greater impact on daily living).

Results of the pilot study suggested that variables included in the revised measure displayed appropriate item performance, the scaled symptom and impact modules exhibited strong measurement properties, and the elements of the STATE survey had the potential to differentiate between patients with varying levels of statin-related side effects.

Stage 3: Population-level evaluation in large commercial sample

In stage 3 of the STATE survey development, the larger population survey was fielded in the Lightspeed Health (Kantar) commercial panel. The online survey was completed by a sample of people (N = 1500) who self-reported high cholesterol. Screening questions further specified the participants to have taken a statin within the past 2 years and to have had $\geq$ 1 statin-associated adverse experience in the last 6 months. Patients who were currently taking or had recently discontinued a statin medication were further identified. The STATE survey fielded in the larger population study retained the same 6 domains as the pilot survey (demographics; clinical characteristics; health knowledge and beliefs; statin history; statin symptom severity; and impact of statins on activities of daily living). A copy of the final version of the survey is available on request.

Statistical analysis

Standard descriptive statistics (such as mean, standard deviation, minimum/maximum for continuous variables, and the frequency and distribution of responses for categorical variables) were examined, as were correlation

matrices among related variables to characterize the item-level performance of variables included in the STATE survey. The item-level performance of the Symptom and Impact Severity Scales within the STATE survey was evaluated through classical test theory psychometric analyses and item-reduction methods and Rasch measurement theory analyses. Bivariate comparisons (*t*-tests and chi-square tests) were used to identify those variables from the STATE survey that showed evidence of differentiation between patients who discontinued statins vs those who continued statin use despite having signs and symptoms.

Results

Sample selection, demographics, and clinical characteristics

Of the total 43,053 individuals with self-reported high cholesterol invited to complete the STATE survey, 1500 had taken a statin in the last 2 years and experienced ≥ 1 statin-associated symptom in the last 6 months (Fig. 1). Mean age was 58 years, and 40.3% were men (Table 1). Nearly half (43.2%) had tried ≥ 2 statins, and many had high-risk clinical comorbidities such as ASCVD (22.5%), diabetes (25.8%), and hypertension (56.0%). Most respondents (77.9%) were currently taking a statin; 22.1% had discontinued statin therapy.

Reasons for continuing or discontinuing statin therapy

To understand more about the main reasons people had for wanting to continue to take statins despite some adverse experiences and for deciding to stop taking statins, respondents were asked to rank the importance of a list of the reasons influencing these decisions (Fig. 2). Prevention of heart attack/stroke was ranked as the most important reason for taking statins despite symptoms (mean ranking = 8.48), followed by lowering cholesterol (mean ranking = 8.34), doctor recommendation (mean ranking = 8.32), perceived high-risk of heart disease (mean ranking = 6.91), and family history of heart disease (mean ranking = 6.38). Of those who stopped statin therapy, being bothered by (mean ranking = 7.10) or unable to tolerate (mean ranking = 6.70) their side effects were ranked as the most important reasons for discontinuing treatment. Moreover, too much interference with daily life (mean ranking = 6.48) and risk of side effects not worth the level of the patient's cardiovascular risk (mean ranking = 6.15) were other important reasons for stopping statin therapy.

Symptom and impact severity scores by statin use

Survey participants were asked to rate the severity of their statin-associated symptoms (Symptom Severity Scale) at their very worst (eg, muscle complaints, joint or bone complaints) and to rate the degree of difficulty that their statin-related symptoms had on their everyday life (Impact Severity Scale). For all symptoms except memory problems and tiring easily, significantly higher percentages of patients who stopped statins experienced severe or very severe symptoms compared with those who experienced similar symptoms yet continued to take their statin (Table 2). In addition, those who stopped taking their statin because of symptoms were more likely to report significantly greater impact severity and difficulty in all items that assessed the impact on activities of daily living (eg,

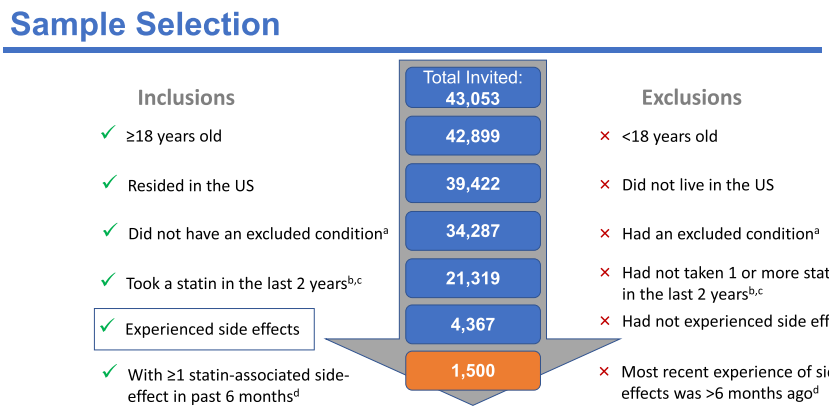

Figure 1 Sample selection. [a]Excluded conditions included fibromyalgia, multiple sclerosis, muscular dystrophy, untreated thyroid disease, liver disease, kidney disease requiring dialysis, and any condition requiring treatment with corticosteroids or cyclosporine. [b]Statins: atorvastatin (Lipitor), cerivastatin (Baycol), fluvastatin (Lescol, Lescol XL), lovastatin (Mevacor, Altoprev), pitavastatin (Livalo), pravastatin (Pravachol), rosuvastatin (Crestor), and simvastatin (Zocor). Statin combination drugs: atorvastatin-amlodipine (Caduet), atorvastatin-ezetimibe (Liptruzet), lovastatin-niacin (Advicor), simvastatin-ezetimibe (Vytorin), and simvastatin-niacin (Simcor). [c]25.1% (n = 10,785) were never prescribed a statin drug, 1.3% (n = 577) were prescribed a statin but did not take the medication, and 3.7% (n = 1606) took a statin previously but not in the past 2 years. [d]A 6-month cutoff was selected to minimize recall bias, given that patients self-reported these experiences.

Table 1 Demographics and clinical characteristics

Characteristics	Currently taking statin N = 1168	Stopped statin N = 332	Overall N = 1500
Age, years			
Mean (SD)	58.1 (13.0)	58.3 (13.4)	58.1 (13.1)
Median	60.0	61.0	60.0
Age category, years, n (%)			
18–24	8 (0.7)	6 (1.8)	14 (0.9)
25–34	59 (5.1)	11 (3.3)	70 (4.7)
35–44	122 (10.4)	38 (11.4)	160 (0.7)
45–54	211 (18.1)	61 (18.4)	272 (18.1)
55+ (oldest, 91 y)	768 (65.8)	216 (65.1)	984 (65.6)
Sex, n (%)			
Men	480 (41.1)	124 (37.3)	604 (40.3)
Race, n (%)[a]			
White	1041 (89.1)	294 (88.6)	1335 (89.0)
Black or African American	76 (6.5)	26 (7.8)	102 (6.8)
American Indian or Alaska Native	24 (2.1)	11 (3.3)	35 (2.3)
Native Hawaiian or other Pacific Islander	2 (0.2)	3 (0.9)	5 (0.3)
Middle Eastern or North African	1 (0.1)	0	1 (0.1)
Asian Indian or South Asian East	4 (0.3)	1 (0.3)	5 (0.3)
Asian	22 (1.9)	4 (1.2)	26 (1.7)
Other	21 (1.8)	5 (1.5)	26 (1.7)
Ethnicity, n (%)			
Hispanic, Latino, or Spanish origin	143 (12.2)	41 (12.3)	184 (12.3)
Statin history, n (%)			
Tried 1 statin	654 (56.0)	198 (59.6)	852 (56.8)
Tried ≥ 2 statins	514 (44.0)	134 (40.4)	648 (43.2)
Cardiovascular comorbidities, n (%)			
Diabetes	312 (26.7)	75 (22.6)	387 (25.8)
Heart attack	104 (8.9)	21 (6.3)	125 (8.3)
Heart disease	179 (15.3)	36 (10.8)	215 (14.3)
Hospitalized for heart procedure	129 (11.0)	29 (8.7)	158 (10.5)
High blood pressure/hypertension	662 (56.7)	178 (53.6)	840 (56.0)
Peripheral vascular disease	21 (1.8)	5 (1.5)	26 (1.7)
Stroke	47 (4.0)	18 (5.4)	65 (4.3)
ASCVD[b]	268 (22.9)	70 (21.1)	338 (22.5)
ASCVD with diabetes[c]	101 (8.6)	13 (3.9)	114 (7.6)
Coronary heart disease[d]	231 (19.8)	55 (16.6)	286 (19.1)

ASCVD, atherosclerotic cardiovascular disease.

[a]Respondents were instructed to select all that apply; therefore, percentages may total more than 100%.

[b]ASCVD was defined as 1 or more of the following 5 options: heart attack, heart disease, hospitalized for heart procedure, peripheral vascular disease, and stroke.

[c]$P < .05$ for comparison between those who were currently taking and those who had stopped statin therapy.

[d]Coronary heart disease was defined as 1 or more of the following 3 options: heart attack, heart disease, and hospitalized for heart procedure.

physical activity, rest, productivity, sleep) when compared with those having similar symptoms who continued to take their statin (Table 3). Supplemental Appendix 2 (See Q20 and Q21) provides a full summary of all patient-reported statin Symptom Severity and Impact Severity items across all severity options.

To assess the overall extent of statin-related symptom severity and impact on daily life, total summary scores were generated for the Symptom Severity (sum of the 8 items with score ranging between 0 [none] and 32 [very severe symptomatology]) and the Impact Severity (sum of the 6 items with score ranging between 0 [no difficulty] to 24 [extremely difficult]) measures of the survey. Respondents who had stopped their statin therapy reported significantly higher symptom (Fig. 3A) and impact (Fig. 3B) scores from their medication, indicating greater symptomatology and effects on daily living. Supplemental Appendix 2 provides full item-level data for both PRO measures (Q20 and Q21).

Patient-reported treatment regimen changes

Of respondents currently taking statin therapy who experienced side effects or abnormal laboratory values, 40.2% were able to avoid discontinuation with regimen changes such as reducing the dose (22.6%) and/or

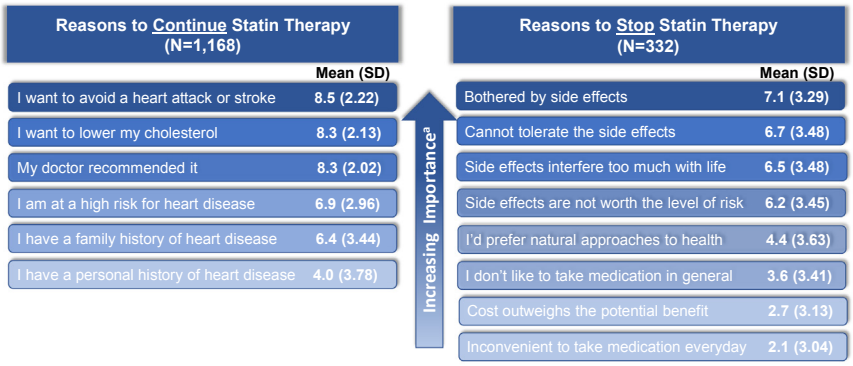

Figure 2 Key reasons to continue or stop statin therapy by order of importance. [a]0 = not important at all; 10 = extremely important.

switching statins (24.2%) (Fig. 4). Fewer patients (23.7%) who recently discontinued statin therapy had any changes to their regimen in response to side effects or abnormal laboratory values. Supplemental Appendix (See Q22) provides a full summary of possible responses regarding patient-reported treatment regimen changes.

Patients' willingness to try other options

Several questions in the STATE survey were designed to assess patients' willingness to try other therapeutic options (see Supplemental Appendix 2 for item-level data for the verbatim questions and full response options; Q27, Q27, Q28, Q32, and Q33). Of respondents who stopped statin therapy, nearly half were not taking anything to manage their cholesterol, and 1 in 5 discontinued therapy without informing their provider (Fig. 5). At least half of the respondents who reported that they were not at treatment goal were willing to try other options, such as a different statin or a nonstatin prescription medication to help control their cholesterol.

Discussion

The STATE survey represents a comprehensive effort to use the patient's voice to develop a content-relevant statin experience survey. This survey aimed to describe and assess patients' experiences with statin-associated side effects and the resulting impacts on various aspects of daily life. Compared with prior studies that focused primarily on muscle-related symptoms, such as the USAGE survey and the Statin-Associated Muscle Symptom Clinical Index,[9,11,14,19] the STATE survey is more comprehensive because it was developed specifically to incorporate a wide range of cognitive assessments and behavioral markers in 6 domains across a wide breadth of topics beyond muscle symptoms. One other survey study included a semicomprehensive assessment of patient-reported statin responses, which included quality-of-life measures in addition to muscle-related adverse statin experiences.[20] Similar to the STATE survey, Cham et al[20] concluded that statin-associated muscle symptoms have significant functional and quality-of-life implications; however, the study sample in that case series was passively selected and was considerably smaller (N = 354) than the 1500 respondents who met the inclusion criteria for the STATE survey. Furthermore, the authors did not attempt to identify patients who might be at risk for discontinuing statin therapy, which was an objective unique to the STATE survey.

Although all STATE survey respondents reported at least 1 statin-associated symptom within the past 6 months, a recall duration that was selected to minimize bias for self-

Table 2 Symptom severity: Percentage of patients who rated their symptoms on statin therapy as either "severe" or "very severe"

Symptom items	Stopped statin (N = 332)	Currently taking statin (N = 1168)	*P* value[a]
Severe or very severe, n (%)			
Muscle aches	88 (26.5)	185 (15.8)	<.0001
Muscle cramps	88 (26.5)	226 (19.3)	.005
Muscle pain	88 (26.5)	185 (15.8)	<.0001
Muscle stiffness	60 (18.1)	130 (11.1)	.001
Muscle weakness	61 (18.4)	137 (11.7)	.002
Joint or bone pain	58 (17.5)	141 (12.1)	.011
Memory problems	24 (7.2)	66 (5.7)	.285
Tiring easily	67 (20.2)	197 (16.9)	.162

[a]*P* values from chi-square tests.

Table 3 Impact severity: Percentage of patients who reported that their symptoms on statin therapy caused a "good deal of difficulty" or "great deal of difficulty" in everyday life

Impact items	Stopped statin (N = 332)	Currently taking statin (N = 1168)	*P* value[a]
Good or great deal of difficulty, n (%)			
Needing to rest more	105 (31.6)	301 (25.8)	.034
Reduced ability to be physically active or exercise	147 (44.3)	402 (34.4)	.001
Reduced productivity or performance	137 (41.3)	335 (28.7)	<.0001
Trouble getting good-quality sleep	153 (46.1)	433 (37.1)	.003
Limited social activities	94 (28.3)	227 (19.4)	.001
Increased need to interact with your doctor	94 (28.3)	240 (20.5)	.003

[a]*P* values from chi-square tests.

reported data, 20.5% of those who took a statin in the past 2 years experienced statin-associated symptoms. Overall, our findings are within the range of rates reported for observational studies in the literature and consistent with the PRedIction of Muscular Risk in Observational Conditions survey.[15,21] Moreover, prevalence of statin-related symptoms might be underestimated in the commercial panel because the sample population was younger than the U.S. census population (18% vs 30% ≥ 55 years in the commercial panel vs U.S. census, respectively) and included more women (70% vs 51% in the commercial panel vs U.S. census, respectively).

In the Patient and Provider Assessment of Lipid Management registry, fear of side effects and perceived side effects were the most common patient-reported reasons for declining to take a statin or discontinuing statin therapy.[22] Results of the STATE survey suggest that some patients are motivated to stay on statin therapy even after experiencing symptoms because they want to avoid a heart attack or stroke and they want to lower their cholesterol. For other patients, the side effects of statins are too bothersome, too intolerable, or interfere too much with daily life, and therefore, they discontinue therapy. We observed that 22% of our sample had recently discontinued statin therapy, which is higher than the statin discontinuation rate of approximately 10% reported in other observational studies, including the USAGE survey.[9–12] The Symptom Severity and Impact Severity PROs in the STATE survey were designed to capture the most relevant statin-related symptoms and impacts on daily life, and these severity measures have the potential to differentiate those likely to continue therapy despite symptoms from those at risk for discontinuation of therapy. On both the symptom and impact severity scales, a difference of approximately 2 points in the mean summary score between respondents continuing and discontinuing statin therapy was statistically significant. Furthermore, among patients who stopped statin therapy, the mean score for the impact severity scale was higher than that for the symptom severity scale. This finding emphasizes the importance of issues other than muscle symptoms alone and the overall impact that statin-related symptoms can have on patients' quality of life.

Because studies have shown that the risk of cardiovascular events increases with statin nonpersistence or

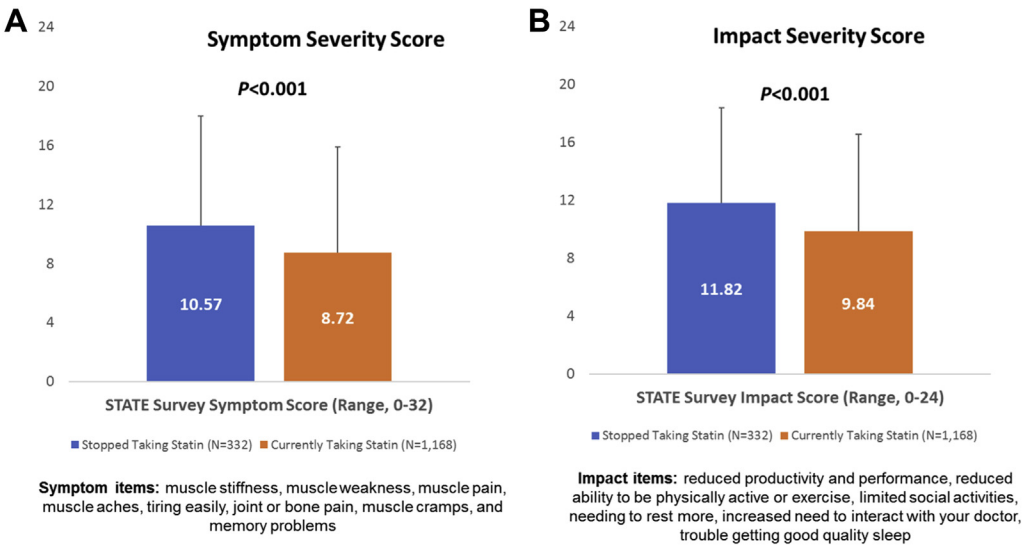

Figure 3 Symptom severity (A) and impact severity (B) scores by statin use.

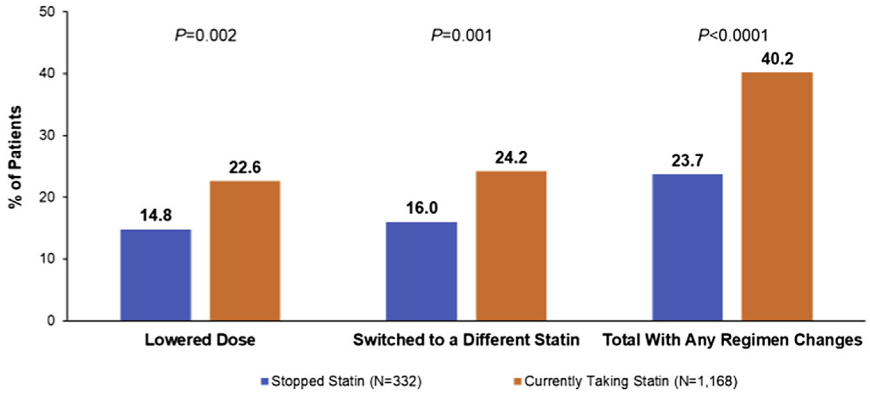

Figure 4 Changes to statin regimen because of side effects or abnormal laboratory results by statin use. "Total with any regimen changes" includes respondents who endorsed either "My dose has been lowered" and/or "I've switched to a different statin," in addition to any of the other possible response options for the question.

underutilization,[23–25] it is important for clinicians to reliably identify patients who might be at risk for stopping their statin therapy. Data from the STATE survey indicate that many patients who experience statin-related side effects can stay on their treatment when their regimens are modified. Once a patient reports statin-related symptoms, it is essential for providers to work with the patient to minimize the risk of discontinuing therapy and adjust their regimens accordingly. In 1 real-world clinical practice study, 92% of patients could tolerate a second statin after discontinuing their initial statin.[10] In the Patient and Provider Assessment of Lipid Management registry, 59.7% of patients who previously discontinued statin therapy were willing to retry a statin.[22] In addition, Hovingh et al[12] reported that although 71% of statin-treated patients in the United States develop potentially statin-associated muscle symptoms, only 6% were considered statin-intolerant after modifications such as reducing the dose, temporary discontinuation and rechallenge, or trying at least 2 statins.[12] Most physicians surveyed reported that approximately half of their statin-intolerant patients continued to receive low-dose statins, usually in combination with other lipid-lowering therapies; 38% were treated with other, nonstatin therapies; and 11% received no subsequent lipid-lowering therapy.[12] For patients who cannot tolerate recommended doses of statin therapy and for very high-risk patients who are not meeting LDL-C goals, physicians should also consider nonstatin therapies such as cholesterol absorption inhibitors and proprotein convertase subtilisin/kexin type 9 inhibitors, which have been proven to reduce cardiovascular events in addition to maximally tolerated statin therapy.[1,26–28]

To our knowledge, the STATE survey represents the first attempt to develop a statin survey based on a comprehensive set of patient experiences and behavioral markers. Strengths of the survey include that it was developed using the patient's voice and that it was rigorously validated; information collected during the cognitive interviews was validated in a pilot study, and items were then revised before being fielded for quantitative assessment in a large commercial sample. In addition, the quantitative study was recently conducted in 2018 to reflect current clinical practice patterns and included many patients with comorbidities that put them at risk for cardiovascular disease. Limitations include possible selection bias in the panel-

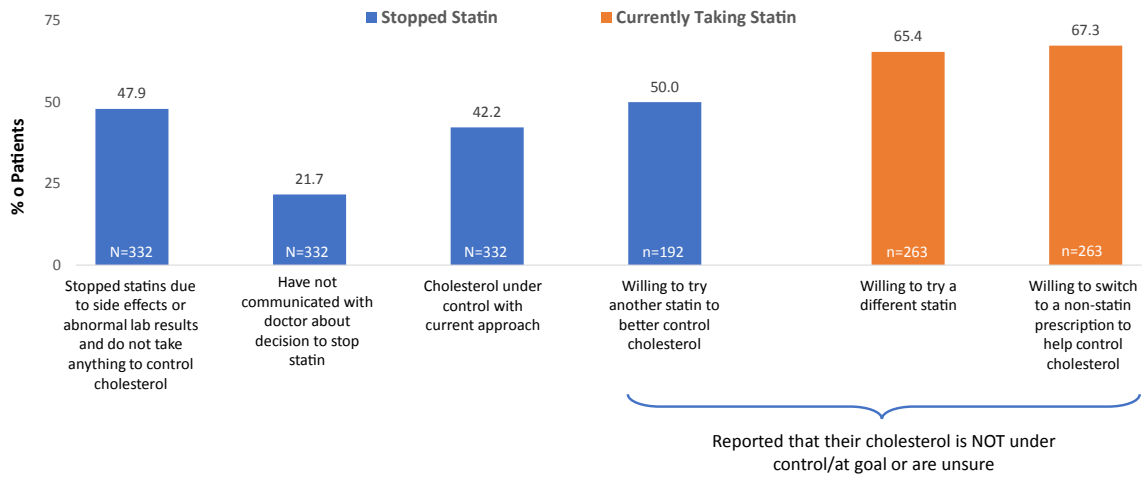

Figure 5 Willingness to try other treatment options.

based market research sample. Generalizability to the broader population of statin users in the United States and racial and ethnic minorities may be limited, in part because the commercial sample was mostly white/non-Hispanic and included more women than men.

Future research to leverage the full scope of data collected in the STATE survey could include additional subgroup analyses to further characterize statin symptom and impact severity in high-risk patients with ASCVD and/or those who had tried 1 vs $\geq$ 2 statins. In addition, the STATE survey could provide a foundation for the development of a patient-reported survey tool for use in clinical practice. Such a tool could potentially be used to identify patients whose clinical and demographic characteristics are similar those who discontinued statin treatment in the STATE survey. Clinicians could then initiate benefit-risk discussions with patients who may be having difficulty with their current statin regimen and proactively take action to modify the dose, try a different statin, or initiate other treatment options to improve treatment adherence and promote a positive impact on patient outcomes.

Conclusions

The STATE survey represents a comprehensive effort to develop a statin survey based on the patient's voice, which also assesses the impact of statins on daily life. The STATE survey highlights the importance of patients' adverse experiences with statins and how symptom and impact scores can affect their decision to continue or discontinue statin therapy. These data provide a foundation to increase providers' awareness of statin tolerability from the patient's perspective and encourage risk-benefit discussions, with the ultimate goal of keeping patients on effective lipid-lowering therapies to prevent cardiovascular events and improve patient outcomes.

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Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing.

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Supplementary data

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References

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2018. https://doi.org/10.1016/j.jacc.2018.11.002. [published online ahead of print November 3, 2018].
2. Stone NJ, Robinson JG, Lichtenstein AH, et al, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart

Association Task Force on practice guidelines. *Circulation*. 2014; 129(25 Suppl 2):S1–S45.
3. Cholesterol Treatment Trialists Collaboration, Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
4. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1–full report. *J Clin Lipidol*. 2015;9:129–169.
5. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. The National Lipid Association's muscle safety expert panel. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S58–S71.
6. Pencina MJ, Navar-Boggan AM, D'Agostino RB, Williams K, Neely B, Sniderman AD, Peterson ED. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med*. 2014;370: 1422–1431.
7. Salami JA, Warraich H, Valero-Elizondo J, et al. National trends in statin use and expenditures in the US adult population from 2002 to 2013: insights from the Medical Expenditure Panel Survey. *JAMA Cardiol*. 2017;2:56–65.
8. Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012. NCHS Data Brief, No 177, Hyattsville, MD; 2014. p. 1–8.
9. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol*. 2012;6:208–215.
10. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med*. 2013;158: 526–534.
11. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education. *J Clin Lipidol*. 2013;7:472–483.
12. Hovingh GK, Gandra SR, McKendrick J, et al. Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey. *Atherosclerosis*. 2016;245:111–117.
13. Adhyaru BB, Jacobson TA. Safety and efficacy of statin therapy. *Nat Rev Cardiol*. 2018;15:757–769.
14. Jacobson TA, Khan A, Maki KC, Brinton EA, Cohen JD. Provider recommendations for patient-reported muscle symptoms on statin therapy: insights from the understanding statin use in America and gaps in patient education survey. *J Clin Lipidol*. 2018;12:78–88.
15. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. *J Am Coll Cardiol*. 2016;67:2395–2410.
16. Serban MC, Colantonio LD, Manthripragada AD, et al. Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. *J Am Coll Cardiol*. 2017;69: 1386–1395.
17. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. 2016;316:1289–1297.
18. Guyton JR, Bays HE, Grundy SM, Jacobson TA. The National Lipid Association Statin Intolerance Panel. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol*. 2014;8: S72–S81.
19. Rosenson RS, Miller K, Bayliss M, et al. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): revision for clinical use, content validation, and inter-rater reliability. *Cardiovasc Drugs Ther*. 2017;31:179–186.
20. Cham S, Evans MA, Denenberg JO, Golomb BA. Statin-associated muscle-related adverse effects: a case series of 354 patients. *Pharmacotherapy*. 2010;30:541–553.
21. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. *Cardiovasc Drugs Ther*. 2005;19: 403–414.
22. Bradley CK, Wang TY, Li S, et al. Patient-reported reasons for declining or discontinuing statin therapy: insights from the PALM registry. *J Am Heart Assoc*. 2019;8:e011765.
23. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J*. 2013;34:2940–2948.
24. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol*. 2014;78:684–698.
25. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388: 2532–2561.
26. Cannon CP, Blazing MA, Giugliano RP, et al, Improve-It Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
27. Sabatine MS, Giugliano RP, Keech AC, et al, Fourier Steering Committee Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376: 1713–1722.
28. Szarek M, White HD, Schwartz GG, et al, Odyssey Outcomes Committees Investigators. Alirocumab reduces total nonfatal cardiovascular and fatal events: the ODYSSEY OUTCOMES trial. *J Am Coll Cardiol*. 2019;73:387–396.