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Muscle symptoms in statin users, associations with cytochrome P450, and membrane transporter inhibitor use: A subanalysis of the USAGE study

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BACKGROUND: Drug interactions have been identified as a risk factor for muscle-related side effects in statin users.

OBJECTIVES: The aim was to assess whether use of medications that inhibit cytochrome P450 (CYP450) isozymes, organic anion transporting polypeptide 1B1 (OATP1B1), or P-glycoprotein (P-gp) are associated with muscle-related symptoms among current and former statin users.

METHODS: Persons (n = 10,138) from the Understanding Statin Use in America and Gaps in Education (USAGE) internet survey were categorized about whether they ever reported new or worsening muscle pain while taking a statin (n = 2935) or ever stopped a statin because of muscle pain (n = 1516). Univariate and multivariate logistic regression models were used to assess associations between use of concomitant therapies that inhibit CYP450 isozymes, OATP1B1, P-gp, or a combination and muscle-related outcomes.

RESULTS: In multivariate analyses, concomitant use of a CYP450 inhibitor was associated with increased odds for new or worse muscle pain (odds ratio [OR] = 1.42; $P < .001$) or ever having stopped a statin because of muscle pain (OR = 1.28; $P = .037$). Concomitant use of medication known to inhibit both OATP1B1 and P-gp was also associated with increased odds (OR = 1.80; $P = .030$) of ever having stopped a statin because of muscle pain.

CONCLUSIONS: Concomitant use of medication(s) that inhibit statin metabolism was associated with increased odds of new or worse muscle pain while taking a statin and having previously stopped a statin because of muscle symptoms. These data emphasize the importance of enhancing the capabilities of clinicians and health systems for identifying and reducing statin drug interactions.

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3-Hydroxy-3-methylglutary coenzyme A reductase inhibitors (statins), are extremely effective drugs for reducing low-density lipoprotein (LDL) cholesterol as well as decreasing the risk of nonfatal myocardial infarction,

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coronary heart disease death, and stroke.[1] Statins inhibit the synthesis of mevalonate, the rate-limiting step in cholesterol biosynthesis, which results in an up-regulation of LDL receptors. Statins are generally well tolerated, but muscle-related side effects are common.[2] In the Understanding Statin Use in America and Gaps in Education (USAGE) survey, muscle-related side effect while taking a statin were reported by 29% of the survey participants.[3,4] In former statin users, 62% of the participants reported side effects (mainly in the muscles) as the primary reason for discontinuation of a statin. The average number of potentially interacting concomitant medication in USAGE was 3.[3] A recent study conducted in the United Kingdom reported that 30% of 364,574 patients taking a statin metabolized by the cytochrome P450 (CYP450) 3A4 system were also co-administered a CYP450 3A4 inhibitor.[5] Drugs that reduce statin metabolism by inhibiting CYP450 isozymes or interfering with drug transporters, such as organic anion transporting polypeptide 1B1 (OATP1B1) and P-glycoprotein (P-gp), can lead to increased systemic exposure of the statin and increase risk of myopathy.[6,7] We hypothesized that among USAGE participants the use of concomitant medication(s) that either inhibit CYP450 isozymes, OATP1B1, or P-gp alone or in their combination would be associated with increased odds of new or worsening muscle pain while taking a statin or ever having stopped a statin because of muscle pain.

Methods

Study design

The study population was derived from participants in the USAGE survey. The USAGE survey was conducted from September 21, 2011, through October 17, 2011, via an Internet-based, self-administered questionnaire developed by Kantar Health (New York, NY), with input from the study investigators representing the National Lipid Association, as well as from Kowa Pharmaceuticals America, Inc (Montgomery, AL) and Eli Lilly and Company (Indianapolis, IN). The survey was administered by Lightspeed Online Research, Inc (New York, NY), a subsidiary of Kantar Health to subjects in their online-registered consumer panel. The study protocol and questionnaire were compliant with the Health Insurance Portability and Accountability Act and were reviewed and approved by the Essex Institutional Review Board (Lebanon, NJ). After field testing the survey to approximately 10% of prequalified persons, all potential respondents were then invited via e-mail to participate. The survey content was not described in the invitation. Persons who expressed a desire to participate were sent a link to a preliminary screening questionnaire to assess whether they met the following inclusion criteria: 18 years of age or older, self-reported diagnosis of a high cholesterol level made by a health care provider, self-reported current or former use of a statin (alone or in combination with another cholesterol-lowering medication), ability to read and write English, and residence in the United States at the time of the study. Respondents who did not meet these inclusion criteria were exited from the survey instrument. Respondents who were eligible were asked to provide informed consent, at which time the topic of the survey was explained, and resources to address any questions or concerns were provided. Current and former statin users who gave informed consent completed the online survey of 89 questions related to demographics; medical history (presence of hypertension, diabetes, cardiovascular disease, etc); comorbidities (mental health conditions, thyroid disease, etc); concomitant medications use, including over-the-counter drugs and dietary supplements; type of statin (branded or generic); lipid treatment history; and muscle symptoms while currently or formerly taking a statin. A total of 10,138 current and former statin users completed the survey, and their data were used for this subanalysis.

Concomitant medications

A list of concomitant medications and dietary supplements was provided on the survey. Each medication was categorized as an inhibitor of CYP450, P-gp, or OATP1B1 and any combination. Determination of inhibitor status was determined by using both Epocrates' RX for Apple iOS (Epocrates, Inc, San Mateo, CA) drug interaction and pharmacology functions[8] and Food and Drug Administration approved prescription drug information. (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) for each medication. A list of concomitant medications that were considered CYP450 3A4, P-gp, and OATP1B1 inhibitors that USAGE participants could choose from are listed in the Supplementary Table.

Data analysis

Descriptive statistics (number of subjects, mean, standard error of the mean, standard deviation, median, interquartile limits, minimum and maximum for continuous variables; counts and percentages for categorical variables) were calculated overall and for subjects categorized according to whether they had reported experiencing new or worsened muscled pain while taking a statin, as well as for those subjects who reported ever having stopped a statin because of muscle pain.

Categorical variables with >2 levels were re-coded with indicator variables for analysis. This was done for race such that a variable was created for black non-Hispanic, yes or no; Hispanic, yes or no; and other, yes or no; with white non-Hispanic as the reference. Body mass index (BMI; calculated as weight divided by height squared; in kg/m^2) was categorized as follows: declined to answer, underweight for BMI <18.5, overweight for BMI ≥ 25 and <30, and obese for BMI ≥ 30, with normal weight for

BMI ≥18.5 and <25 as the reference value. Brand name statin medication vs generic or unknown was re-coded with generic statin as the reference.

Univariate logistic regression analyses were performed to investigate significant predictors of having experienced new or worsened muscle pain on a statin and having stopped a statin because of muscle pain. Potential predictors included demographic variables (age in decades, sex, BMI [underweight, normal weight, overweight, obese, declined to answer], race [non-Hispanic black, non-Hispanic white, Hispanic, other]); medical history (presence of cardiovascular disease, presence of diabetes, presence of hypertension, presence of mental health comorbidities, presence of a thyroid condition, and presence of other comorbidities, ie, not specified as one of those listed); generic, brand name, or unknown statin use; any grapefruit or star fruit juice consumption; as well as concomitant medications classified as inhibitors of CYP450 enzyme pathways (classified as inhibitors of 3A4, 2C9, 1A2, 2C19, 2C8, 2B6, 2D6, 1A1, or 1A9), P-gp, and OATP1B1, as well any combination of these inhibitors of OATP1B1 + P-gp (no subjects were taking this combination), CYP450 + OATP1B1 + P-gp (no subjects were taking this combination), CYP450 + OATP1B1 (no subjects were taking this

Table 1 Patient demographics and clinical characteristics of USAGE population

	All respondents	Ever experienced new or worsening muscle pain while taking a statin	Ever stopped statin because of muscle pain
Number of subjects	10,138	2935	1516
Age, year, mean ± SEM	61.0 ± 0.1	61.0 ± 0.2	62.0 ± 0.2
BMI, mean ± SEM	30.6 ± 0.1	30.8 ± 0.1	30.3 ± 0.2
Weight, kg, mean ± SEM	87.8 ± 0.2	87.8 ± 0.4	85.7 ± 0.6
Race (%)			
Black non-Hispanic	1.6	1.4	1.4
Hispanic	1.0	1.3	1.0
Other	5.1	5.2	5.0
White non-Hispanic	92.3	92.1	92.7
Sex, %			
Female	60.6	64.9	69.5
Male	39.4	35.1	30.5
BMI categories, %			
Underweight	0.4	0.4	0.6
Normal	18.3	17.0	19.4
Overweight	33.7	33.1	33.7
Obese	44.0	46.0	42.6
Concomitant conditions, %			
Cardiovascular disease	6.9	9.3	8.8
Diabetes	27.7	27.9	25.5
Hypertension	65.8	65.7	63.1
Mental health comorbidity	20.3	23.1	20.2
Thyroid disorder	17.4	20.2	22.4
Other comorbidities	58.0	64.5	65.2
Grapefruit or star fruit juice use	18.3	18.4	16.6
Generic vs brand statin, %			
Brand	31.3	28.6	25.3
Do not know	1.0	1.3	0.9
Generic	53.3	45.1	31.9
NA	12.0	25.1	41.8
Concomitant inhibitors of CYP450 or transporters, %			
CYP450 only	6.8	8.9	8.2
P-gp only	5.4	6.2	6.1
OATP1B1 only	0.02	0.03	0
CYP450 + P-gp	0	0	0
CYP450 + P-gp + OATP1B1	0	0	0
CYP450 + OATP1B1	0	0	0
P-gp + OATP1B1	1.0	1.1	1.5
CYP450 3A4	3.7	4.5	4.4
CYP450 excluding 3A4	8.0	10.1	9.0

BMI, body mass index (calculated as weight divided by height squared; kg/m^2); CYP450, cytochrome P450; NA, not applicable; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein.

combination), and OATP1B1 + P-gp. Because only 2 subjects were taking OATP1B1 inhibitors alone, this category was combined with OATP1B1 + P-gp.

If a variable had a P value $\leq .10$ in the univariate analysis, it was included as a candidate variable in multivariate modeling for that outcome. Multivariate models were reduced in a backward, stepwise fashion to include variables significant at the $\alpha = 0.10$ level. For the indicator variables, if 1 level of the variable was significant, all levels were retained in the model. Odds ratios (ORs), 95% confidence intervals, and P values for predictor variables were generated for both the univariate and multivariate models.

Results

Demographic and clinical characteristics of the full sample of respondents, as well as respondents who reported ever having experienced new or worsened muscle pain on statin, and respondents who reported ever having stopped a statin because of muscle pain are presented in Table 1. Approximately 29% of the USAGE participants reported ever having experienced new or worsened muscle pain while taking a statin and approximately 15% ever stopped a statin because of muscle pain. Overall, USAGE respondents were generally older (mean age, 61 years), obese (mean BMI, 30.6), primarily white (92%), and 61% were women. The most frequent concomitant medical conditions were hypertension, diabetes, and mental health disorders. Approximately 18% of the respondents reported using any grapefruit or star fruit juice.

Concomitant use of medication known to inhibit only CYP450 enzymes in all USAGE respondents, respondents who ever experienced new or worsening muscle pain while taking a statin, and respondents who ever stopped statins because of muscle pain was 6.8%, 8.9%, and 8.2%, respectively, and medications that inhibit CYP450 3A4 only were 3.7%, 4.5%, and 4.4%, respectively. Concomitant use of medications known to inhibit P-gp only were 5.4%, 6.2%, and 6.1%, respectively, and medications that inhibit OATP1B1 only was very low (≤0.03%). No patients were taking concomitant medications known to inhibit CYP450, P-gp, and OATP1B1. Less than 1.5% of patients

Table 2 Univariate and multivariate analysis ever experienced new or worse muscle pain on a statin

	Univariate analysis		Multivariate analysis	
Variable	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age (decades)	1.07 (1.03–1.12)	.0014	1.12 (1.07–1.18)	<.0001
Body mass index categories (reference = normal weight)*				
Declined to answer	1.07 (0.83–1.38)	.5900	1.08 (0.83–1.40)	.5789
Obese	1.17 (1.04–1.32)	.0103	1.27 (1.12–1.45)	.0002
Overweight	1.07 (0.94–1.22)	.2802	1.16 (1.01–1.32)	.0314
Underweight	1.13 (0.59–2.18)	.7071	0.86 (0.43–1.73)	.6665
Cardiovascular disease	1.66 (1.42–1.95)	<.0001	1.56 (1.31–1.85)	<.0001
Other comorbidities	1.46 (1.34–1.60)	<.0001	1.26 (1.14–1.39)	<.0001
Diabetes†	1.01 (0.92–1.11)	.7928	–	–
Female	1.29 (1.18–1.41)	<.0001	1.25 (1.13–1.38)	<.0001
Grapefruit or star fruit juice†	1.01 (0.91–1.13)	.8276	–	–
Hypertension*,†	1.00 (0.91–1.09)	.9217	–	–
Inhibitors*				
OATP1B1 + P-gp	1.24 (0.81–1.91)	.3155	1.12 (0.72–1.76)	.6113
P-gp only	1.23 (1.02–1.48)	.0263	1.20 (0.99–1.46)	.0625
CYP450 only	1.55 (1.32–1.83)	<.0001	1.42 (1.20–1.69)	<.0001
Mental health comorbidity	1.27 (1.14–1.41)	<.0001	1.16 (1.03–1.30)	.0130
Race (reference = white non-Hispanic)*				
Black non-Hispanic	0.85 (0.60–1.21)	.3586	0.84 (0.58–1.22)	.3637
Hispanic	1.45 (0.98–2.17)	.0652	1.54 (1.01–2.34)	.0461
Other	1.03 (0.85–1.25)	.7817	1.13 (0.92–1.38)	.2518
Statin therapy (reference = taking a generic statin)*				
Brand name statin	1.17 (1.05–1.29)	.0028	1.15 (1.04–1.27)	.0087
Not on statin therapy	4.92 (4.32–5.61)	<.0001	5.11 (4.47–5.83)	<.0001
Unknown	1.14 (0.78–1.67)	.4966	1.17 (0.80–1.71)	.4305
Thyroid condition	1.30 (1.17–1.45)	<.0001	1.15 (1.02–1.30)	.0200
Weight (5-kg increment)†	1.00 (0.99–1.01)	.8586	–	–

CYP450, cytochrome P450; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein.

*If any level of a categorical variable was significant, all levels were included in the model.

†Terms not significant at the $\alpha = 0.10$ level in the univariate model were not included in the multivariate model.

were taking medications known to inhibit P-gp and OATP1B1.

Table 2 lists the variables tested with univariate and multivariate analyses to assess associations with ever having experienced new or worse muscle pain on a statin. Increasing age and weight (overweight and obese categories), history of cardiovascular disease, history of mental health disorders, female sex, Hispanic ethnicity, taking a brand name statin, not currently being on a statin, and thyroid conditions were associated with increased odds of ever having experienced new or worse muscle pain on a statin in multivariate analyses.

In addition, concomitant use of a CYP450 inhibitor was associated with new or worse muscle pain while on a statin in univariate analysis (OR = 1.55; $P < .0001$), as well as multivariate analyses (OR = 1.55; $P < .0001$). Use of drugs that inhibit only P-gp was associated with increased odds for new or worse muscle pain (OR = 1.23; $P = .0262$) in the univariate analysis, but this association lost statistical significance in the multivariate analysis ($P = .0625$).

Variables tested in univariate and multivariate analyses to assess associations with ever having stopped a statin because of muscle pain while on a statin are shown in Table 3. Increasing age, history of cardiovascular disease, female sex, taking a brand name statin, not currently being on a statin, and the presence of a thyroid conditions were associated with significantly increased odds of ever stopped a statin because of muscle pain while on a statin.

In multivariate analyses, concomitant use of a CYP450 inhibitor was associated with increased odds for new or worse muscle pain (OR = 1.42; $P < .001$) and ever having stopped a statin because of muscle pain (OR = 1.28; $P = .037$). Concomitant use of medication known to inhibit both OATP1B1 and P-gp was also associated with increased odds (OR = 1.80; $P = .030$) of ever having stopped a statin because of muscle pain.

Discussion

Statins significantly reduce cardiovascular events in a broad range of patients with hyperlipidemia.[1] Approximately 20 million patients in the United States take statins,[9] but it has been reported that 10% to 20% of patients who

Table 3 Univariate and multivariate analysis ever stopped a statin because of muscle pain on a statin

	Univariate analysis		Multivariate analysis	
Variable	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age (decades)	1.14 (1.07–1.20)	<.0001	1.23 (1.15–1.31)	<.0001
Body mass index categories (reference = normal weight)*,†				
Declined to answer	0.97 (0.71–1.32)	.8307	–	–
Obese	0.90 (0.77–1.04)	.1548	–	–
Overweight	0.93 (0.80–1.09)	.3779	–	–
Underweight	1.36 (0.65–2.87)	.4131	–	–
Cardiovascular disease	1.40 (1.15–1.70)	.0009	1.48 (1.18–1.86)	.0007
Other comorbidities	1.43 (1.27–1.60)	<.0001	1.17 (1.03–1.33)	.0177
Diabetes‡	0.87 (0.77–0.99)	.0358	–	–
Female	1.58 (1.41–1.78)	<.0001	1.51 (1.32–1.72)	<.0001
Grapefruit or star fruit juice‡	0.87 (0.75–1.01)	.0617	–	–
Hypertension‡	0.87 (0.78–0.98)	.0191	–	–
Inhibitors†				
OATP1B1 + P-gp	1.72 (1.06–2.77)	.0271	1.80 (1.06–3.05)	.0296
P-gp only	1.18 (0.93–1.48)	.1689	1.21 (0.94–1.57)	.1371
CYP450 only	1.28 (1.05–1.57)	.0161	1.28 (1.02–1.61)	.0365
Mental health comorbidity*	0.99 (0.87–1.14)	.9367	–	–
Race (reference = white non-Hispanic)*,†				
Black non-Hispanic	0.83 (0.52–1.32)	.4311	–	–
Hispanic	0.94 (0.54–1.63)	.8337	–	–
Other	0.96 (0.75–1.24)	.7629	–	–
Statin therapy (reference = taking a generic statin)†				
Brand name statin	1.46 (1.27–1.68)	<.0001	1.45 (1.25–1.67)	<.0001
Not on statin therapy	11.45 (9.89–13.25)	<.0001	12.10 (10.42–14.05)	<.0001
Unknown	1.16 (0.66–2.03)	.6085	1.26 (0.72–2.21)	.4269
Thyroid condition	1.45 (1.27–1.66)	<.0001	1.25 (1.08–1.46)	.0036
Weight (5 kg increment)†	0.98 (0.96–0.99)	.0002	–	–

CYP450, cytochrome P450; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein.

*Terms not significant at the $\alpha = 0.10$ level in the univariate model were not included in the multivariate model.

†If any level of a categorical variable was significant, all levels were included.

‡Terms not significant at the $\alpha = 0.10$ level were not retained in the final multivariate model.

have tried them are unable to tolerate them, particularly because of muscle-related side effects.[2]

Of the USAGE participants, 29% reported ever having experienced new or worsened muscle pain while taking a statin and, approximately 15% had stopped taking a statin because of muscle pain at least once. Statin discontinuation, particularly in higher risk patients, has been associated with increased rates of cardiovascular morbidity and mortality.[10] From prior studies, the risk factors for statin-associated myopathy are female sex, hypothyroidism, renal or hepatic dysfunction, ethanol abuse, excessive grapefruit juice consumption, advanced age, and use of interacting medications.[11,12]

Results from the present study are generally consistent with these previous reports, but additional factors were also identified that were associated with increased odds of new or worsened muscle pain. Increasing age and weight, "other" comorbidities, history of cardiovascular disease, history of mental health disorders, female sex, Hispanic ethnicity, taking a brand name statin, not currently on a statin, thyroid conditions, and concomitant use of a CYP450 inhibitor significantly increased the odds of ever having experienced new or worse muscle pain on a statin in the multivariate analysis.

More importantly in the USAGE study, other factors that were significantly associated with discontinuation of statin therapy because of muscle symptoms were identified. In the multivariate analyses, increasing age, "other" comorbidities, history of cardiovascular disease, female sex, taking a brand name statin, not currently taking a statin, thyroid conditions, and concomitant use of drugs that inhibit drug transporters (ie, OATP1B1 + P-gp) or CYP450 enzymes, were associated with significantly increased odds of ever having stopped a statin because of muscle pain while on a statin. This is the first report that we are aware of that has examined patient characteristics and concomitant use of drugs that inhibit either drug transporters and CYP450 enzymes in a multivariate analyses on the odds of ever stopped a statin because of muscle pain in a model that included known risk factors for myopathy. A recent survey of 10,409 French subjects identified 1074 subjects treated with statins. Of these, 104 subjects had muscular symptoms and 30% of those subjects with muscle symptoms discontinued statin therapy. The investigators did not assess factors associated with statin discontinuation secondary to muscular symptoms.[13]

Curiously, we found that patients taking a branded statin were at higher odds of new or worsened muscle pain or of ever having stopped a statin because of muscle pain than were patients taking a generic statin. The USAGE survey was conducted before atorvastatin became a generic medication, so the most widely prescribed generic statins at that time were lovastatin, simvastatin, and pravastatin, with lovastatin and simvastatin having the greatest potential for drug–drug interactions. Because this was a cross-sectional survey, participants indicated the statin they were taking at the time of the survey, not which statin was associated with muscle symptoms. We conjecture that the reason branded statin use was associated with higher odds of muscle-related side effects was because, after the adverse events occurred, participants may have been subsequently switched to a branded statin.

Branded statins available at the time of this survey were atorvastatin, pitavastatin, and rosuvastatin, which have a lower potential for drug–drug interactions than do lovastatin and simvastatin[5] and appear to be less predisposed to the effects of genetic mutations in OATP1B1 which has been associated with an increased risk of myopathy.[14–17]

Our findings emphasize the importance of clinicians recognizing and minimizing the potential for statin drug interactions, because use of such drugs was not only associated with increased odds of experiencing new or worse muscle pain but also with as much as an 80% increase in the odds of statin discontinuation because of muscle pain. Realizing the potential for improved cardiovascular disease outcomes with statin therapy requires that patients continue taking them. Thus, it is imperative that clinicians use effective methods to anticipate, identify, and alleviate statin drug interactions. Unfortunately, despite the widespread use of pharmacy clinical decision support software that contains drug–drug interaction information, a recent report found that as many as 20% of significant statin–drug interactions were missed in 64 pharmacies.[18]

Hispanics had a higher odds (OR = 1.54; $P = .0461$) of experiencing a new or worse muscle pain than did white non-Hispanics. However, they were not at increased odds of statin discontinuation because of muscle pain. We are not aware of other reports that suggest Hispanics are at higher risk of statin-related myopathies. A clinical trial in 696 Hispanic patients at medium-to-high risk of coronary heart disease compared rosuvastatin with atorvastatin in terms of LDL cholesterol lowering for 6 weeks and did not report an unusually high number of myopathy events. Serious adverse events occurred in <2.5% of patients and discontinuation for myalgia occurred in 4 patients (0.57%).[19] In addition, the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trail Evaluating Rosuvastatin) trial reported that serious adverse event rates were generally lower among blacks and Hispanics than among whites.[20] The JUPITER trial was a randomized, double-blind, placebo-controlled evaluation of rosuvastatin 20 mg in the primary prevention of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, and cardiovascular death and included 12,683 whites and 5117 non-whites with LDL cholesterol levels <130 mg/dL and high-sensitivity C-reactive protein levels ≥2.0 mg/L.

Our study has several limitations. Medication history was obtained with a single category for the calcium channel blockers, fibrates, and proton pump inhibitors. Because of our inability to distinguish among heterogeneous medications in these classes, we excluded these 3 drug classes from this USAGE subanalysis. This likely altered the prevalence of drug interactions in our study, because

7.3% of our subjects were taking a calcium channel blocker, 5.1% were taking a fibrate, and 16.3% were taking a proton pump inhibitor. It is difficult to speculate on what effects this may have had on the study findings, because verapamil and diltiazem are both inhibitors of CYP450 3A4 and P-gp and gemfibrozil inhibits OATP1B1, P-gp, CYP2C8, and the glucuronidation of most statins. We did not ask patients the brand name of their statins or dose; thus, we could not assess whether muscle symptoms were more likely to occur in those statins metabolized by the CYP 450 system or those statins with minimal CYP metabolism (pravastatin, rosuvastatin, pitavastatin) or were dose related. Our data are self-reported, and some misclassification may have occurred. As an example, a review of respondents who reported taking Vytorin (ezetimibe + simvastatin) showed that some classified themselves as taking a brand name statin (70%) and others as taking a generic statin (19%) or did not know (11%). Sensitivity analyses in which all subjects taking Vytorin were classified as taking a generic statin did not materially alter the results (data not shown). Therefore, we do not believe that misclassification had a large effect on the point estimates for the associations presented. The participants in USAGE were 92% white (4% black/African American, 1% Asian or Pacific Islander, and 1% Hispanic); therefore, they may not be representative of the US population.[3] The disposition of statins, primarily rosuvastatin, can be influenced by ethnicity with an increased systemic exposure reported in Asians compared with whites. The initiation dose of 5 mg for rosuvastatin is recommended in Asian patients to compensate for this difference in exposure.[21] It is conceivable that our results may underestimate the effect of statin–drug interactions on muscle-related outcomes if a more diverse population had been studied. Finally, in any cross-sectional survey it is difficult to establish the time sequence of events. As discussed earlier, this may explain why we found that patients taking a brand name statin were at higher odds of new or worsened muscle pain or ever stopped a statin because of muscle pain than for a generic statin. Additionally, prospective data will be required to further define and validate the incidence of such drug–drug interactions and other elements of these relationships such as strength and dose–response characteristics. We are hopeful that the findings reported from this analysis of the USAGE survey will stimulate interest in addressing these questions by other investigators.

Conclusion

The USAGE subanalysis confirms the importance of statin drug interactions as a predictor of the occurrence of muscle pain while taking a statin and stopping statin therapy because of muscle pain. Statins are predominately metabolized by the CYP450 enzyme system and use various drug transporter systems for influx and efflux across cell membranes. Concomitant use of medications that inhibit these important systems was associated with significantly increased odds of new or worse muscle pain and for stopping a statin because of muscle symptoms. These data emphasize the importance of enhancing the capabilities of clinicians and health systems for identifying and reducing statin drug interactions.

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Supplementary data

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