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GATM polymorphism associated with the risk for statin-induced myopathy not replicated in case-control analysis of 715 dyslipidemic individuals

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Summary

Statin-induced myopathy (SIM) is the most common reason for discontinuation of statin therapy. A polymorphism affecting the gene encoding glycine amidinotransferase (*GATM* rs9806699 G>A) was previously associated with reduced risk for SIM. Our objective was to replicate the *GATM* association in a large, multicenter SIM case-control study. Mild and severe SIM cases and ageand gender-matched controls were enrolled. Participants were genotyped, and associations were tested (n=715) using chi-square and logistic regression with consideration for SIM severity and exclusion of subjects with potentially confounding co-medications. The minor allele (A) frequencies of *GATM* rs9806699 in the controls (n=106), mild SIM (n=324), and severe SIM (n=285) cases were 0.26, 0.28, and 0.29, respectively (p=0.447). The unadjusted odds ratio for the A allele for any SIM (mild or severe) was 1.14 (0.82–1.61; p=0.437), which remained non-

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significant in all models. Our results do not replicate the association between *GATM* rs9806699 and SIM.

Introduction

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are highly effective in reducing the risk for major cardiovascular events. The most common reason Americans discontinue their statin therapy is muscle-related side effects (Cohen et al., 2012), or statin-induced myopathy (SIM). SIM can range in severity from mild, tolerable symptoms to life-threatening rhabdomyolysis. Rhabdomyolysis is rare (0.1% frequency), but SIM has been reported by up to 25% and 60% of current and former statin users, respectively (Cohen et al., 2012). Until the factors for predicting SIM are characterized, patients will continue to experience SIM at unacceptably high rates or experience unnecessary cardiovascular events (as a result of discontinuation of their statin therapy) (McGinnis et al., 2009; Simpson and Mendys, 2010; The West of Scotland Coronary Prevention Study Group, 1997).

Mangravite et al. (2013) recently reported a potential genetic marker for decreased risk of SIM. Using gene expression profiling of lymphoblastoid cell lines (LCLs), they identified an interaction between a cis-eQTL for the glycine amidinotransferase gene (GATM; rs9806699; G>A) and simvastatin exposure (Mangravite et al., 2013). Glycine amidinotransferase is the rate-limiting enzyme required for creatine biosynthesis. Creatine is predominantly synthesized in the liver and kidneys and is subsequently transported to skeletal muscle, providing an important source of cellular energy. The A allele was associated with a greater decrease in GATM RNA expression in simvastatin-exposed LCLs compared to non-exposed control LCLs. Mangravite et al. (2013) subsequently translated these *in vitro* findings, investigating the effect of the GATM rs9806699 G>A polymorphism in two independent clinical studies (total SIM cases n = 172). The A allele was significantly associated with decreased risk of SIM (meta-analysis odds ratio = 0.60; 95% confidence interval = 0.45-0.81; $p = 6 \times 10^{-4}$). Mangravite et al. (2013) hypothesized that the observed protective effect of the A allele results from the attenuation of the cellular processes necessary for SIM development, and the attenuation results from the diminished myocellular capacity to store energy as phosphocreatine (as a result of decreased creatine availability) associated with the GATM A allele. In a previous issue of Cell Metabolism, Ballard and Thompson (2013) detail and explore the mechanism proposed by Mangravite et al. (2013), concluding that additional investigation is necessary in order to determine the significance of GATM rs9806699 in the development of SIM. A protective effect of GATM rs9806699 was not identified in a prior genome-wide association study (GWAS) (SEARCH Collaborative Group et al., 2008) and, furthermore, GATM deficiency has been identified as a contributing factor of myopathy (Edvardson et al., 2010).

Two replication studies by Carr et al. (2014) (n = 150 SIM cases) and Floyd et al. (2014) (n = 175 SIM cases) did not replicate the association reported by Mangravite et al. (2013). Carr et al. (2014) reported an odds ratio = 0.94 (p = 0.68) and Floyd et al. (2014) reported an odds ratio = 0.94 (p = 0.68) and Floyd et al. (2014) reported an odds ratio = 0.84 (95% CI = 0.52-1.36; p = 0.49; excluding fibrate users) for the *GATM*

rs9806699 A allele. Fixed-effect meta-analyses by both Floyd et al. (2014) and Mangravite et al. (2014) both yielded null associations for rs9806699. The following hypotheses have been proposed to explain the failed replications of the *GATM* rs9806699 association with SIM: 1) low power to detect a modest effect size; 2) the A allele is only protective against mild SIM; 3) the association is masked by confounding co-medications; and 4) patient heterogeneity. An adequately powered study of well-characterized SIM cases is necessary for a more definitive understanding of the clinical validity of *GATM* rs9806699 and SIM. Herein we address the hypotheses for failed replication of *GATM* rs9806699 and SIM in our own replication study, using a large, multicenter, independent case-control study that includes both mild and severe SIM.

Results

A total of 836 participants were enrolled in this multicenter, case-control study of SIM. Controls were treated with statin therapy for at least 12 months without myopathic symptoms. To enter the study, the participants could have been physician-referred (53%) or self-referred (47%), but the SIM phenotype was evaluated via the same questionnaire in all participants, regardless of the mode of study entry. Caucasian participants with known statin treatment and GATM rs9806699 genotype were included in the analysis (n = 715). Analysis of other racial/ethnic groups was underpowered due to small sample sizes (n < 50 in each non-Caucasian racial/ethnic group). The GATM rs9806699 polymorphism was in Hardy-Weinberg equilibrium in the Caucasian subjects (p = 0.270). Participant characteristics stratified by GATM rs9806699 genotypes and SIM status are displayed in Table 1. The differences in the characteristics and sample sizes between the cases and controls were eliminated in a propensity-matched dataset (see Supplemental Information Table S1). The GATM rs9806699 minor allele and genotype frequencies in the controls, mild SIM, and severe SIM cases are displayed and compared in Table 2. No significant differences in GATM rs9806699 allele or genotype frequencies were found in the complete analytical dataset (n = 715), in the sub-group of subjects without potentially confounding comedications (n = 386), or in the propensity-matched dataset (n = 188). The GATM rs9806699 polymorphism was not significantly associated with SIM (mild and severe combined), mild SIM alone, or severe SIM alone in the complete analytical dataset (n =715), the limited dataset of subjects without potentially confounding co-medications (n =386), or the propensity-matched dataset (n = 188) (Table 3). A summary of all studies investigating the association between GATM variants and SIM is displayed in the Supplemental Data Table S2, and the results for a fixed-effects meta-analysis for rs9806699 are presented in Figure 1. The meta-analysis yielded a marginal, but still null, association between *GATM* rs9806699 and SIM: odds ratio = 0.82 (95% CI = 0.66–1.02; p = 0.072).

Discussion

The protective effect of *GATM* rs9806699 G>A reported by Mangravite et al. (2013) was not replicated in our case-control analyses of SIM in 715 Caucasians. Our null findings are consistent with those reported in two other recent studies by Carr et al. (2014) and Floyd et al. (2014). Furthermore, our analysis addressed several of the limitations that were proposed as causative for the previously failed replications. Our study has the largest number of SIM

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cases (n = 609) among the previously reported association studies (n = 175 was largest number of SIM cases in the study by Floyd et al. [2014]) and sufficient power to detect at least a 25% reduction in the risk of SIM with GATM rs9806699 (i.e., 80% power to detect an odds ratio 0.75 in our overall sample) (Demidenko, 2007). We tested specifically whether the A allele was protective against mild SIM, severe SIM, or both groups combined. We performed analyses limited to a sub-group of participants without potentially confounding co-medications, and in a propensity-matched dataset in which differences in characteristics and sample sizes between cases and controls were eliminated. In all of these analyses, the association between GATM rs9806699 and SIM reported by Mangravite et al. (2013) was not observed. Notably, a direct comparison of the patient characteristics in our study to the Mangravite et al (2013) study is not possible with the available published data. A few patient characteristics can be found in the original Marshfield (Mareedu et al., 2009) and SEARCH (SEARCH Collaborative Group et al., 2008) publications for the overall patient samples, but the characteristics of the sub-groups used specifically in the Mangravite et al (2013) analysis are unavailable. However some notable differences between our study and the overall Marshfield and SEARCH studies include the statin treatment (our study is the only one to include rosuvastatin) and gender (the SEARCH trial was 83% male).

Adding our data to the previous data by Mangravite et al (2013), Carr et al (2014), and Floyd et al (2014) to a fixed-effect meta-analysis still yielded a null association; although it tended toward significance (p = 0.072). Notably, the Mangravite et al (2013) data from the SEARCH trial could not be included in our meta-analysis because rs9806699 was not genotyped. Other variants in *GATM* in linkage disequilibrium with rs9806699 (rs1719247 and rs1346268) were statistically significant in the SEARCH trial. Because our metaanalysis tended toward significance, it is possible that the addition of the SEARCH trial data to a meta-analysis (if SEARCH had genotyped rs9806699) could have yielded a significant association. Therefore the A allele may have a small protective effect in a limited population of patients not treated with confounding co-medications, but further studies are needed to determine the clinical relevance of that scenario.

Patient phenotypic heterogeneity among studies of *GATM* rs9806699 and SIM (and SIM studies in general) is a major issue. SIM symptoms can include muscle pain, tenderness, stiffness, cramping, weakness, and/or fatigue. Patients often present with muscle symptoms but without creatine kinase (CK) elevations or present with CK elevations and no muscle symptoms (Baker and Samjoo, 2008). No widely accepted standard definition of SIM has been established (Rosenson et al., 2014). The subjective (muscle complaints) and objective (biochemical markers) measures delineating SIM vary significantly among studies (Rosenson et al., 2014). Mangravite et al. (2013) defined cases of SIM as patients with muscle symptoms and serum CK concentrations > 3 times the upper limit of normal (xULN) and >10×ULN. In contrast, our study did not use CK in the definition of SIM because only 34% of the combined mild and severe SIM participants in this retrospective study reported measurement of CK. Arguably, the absence of CK data in our definition of SIM may be a limitation; however, Mangravite et al. (2013) did not find an association between *GATM* rs9806699 and CK concentrations, and CK does not routinely correlate with the presence or severity of muscle symptoms. Furthermore, the current cholesterol treatment guidelines by

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the American College of Cardiology and the American Heart Association recommend monitoring CK levels only after severe muscle symptoms occur. Monitoring CK levels is not performed for the purpose of establishing a diagnosis of SIM but for identifying the presence of rhabdomyolysis (Stone et al., 2014). We argue that any muscle effect severe enough to trigger a decrease or discontinuation of statin therapy is clinically relevant; muscle symptoms in the absence of CK elevations have been documented (Phillips, et al., 2002).

Lack of reproducibility in biomedical research is being increasingly recognized as a major problem (Collins and Tabak, 2014). This is troubling for the research community because it can cause stakeholders, such as patients, clinicians, policymakers, and funding agencies, to lose confidence in biomedical research. Further investigation of potential reasons for the repeated failed replication of the findings by Mangravite et al. (2013) is warranted. The study reported by Mangravite et al. (2013) was robust and of the highest quality: a combination of functional in vitro findings translated to two independent clinical studies. Therefore a false positive finding by Mangravite et al. (2013) is highly unlikely. Alternatively, false null findings by our group, Carr et al. (2014), and Floyd et al. (2014) are also highly unlikely because the association failed replication in three separate clinical studies performed by three independent research groups. A key piece of information that may solve this apparent contradiction is the mechanism by which GATM variation impacts SIM; currently the mechanism can only be hypothesized. Experiments establishing the mechanism of GATM involvement with SIM are necessary and could shed light on the specific conditions, if any, in which GATM affects SIM. If a clear mechanism cannot be established, then the findings by Mangravite et al. (2013) could have been another case of the "winner's curse." The "winner's curse" is a common phenomenon in genetic association literature, in which the initial reported genotype-phenotype association is exaggerated relative to the estimated effect in follow-up studies or cannot subsequently be replicated at all (Talameh and McLeod, 2011; Zollner and Pritchard, 2007).

Notably, our study has certain limitations. The proportion of controls (15%) was small compared to SIM cases (85%). However, we balanced the sample sizes and characteristics of the cases and control using propensity-matching and still found a null association. Controls were defined as participants without myopathic symptoms after six months of statin therapy and monitored for any change in status by questionnaire at 12 months. However, it is possible for the onset of SIM to occur even after 12 months of statin therapy. SIM is exacerbated by exercise (Parker and Thompson, 2012), but exercise was not assessed in this study. Two other polymorphisms in *GATM* (rs1719247 and rs1346268) remained statistically significant in a fixed-effects meta-analysis by Mangravite et al. (2014) for an association with SIM, but only rs9806699 was genotyped in our study. Using 1000 Genomes CEU data, the extent of linkage disequilibrium for both rs1719247 and rs1346268 with rs9806699 is $r^2 = 0.85$ and D' = 1.0. Notably, Floyd et al (2014) also performed fixed-effects meta-analyses for rs1719247 and rs1346268, but they found null associations.

In conclusion, we provide further evidence against an association between *GATM* rs9806699 and SIM in a large, multicenter case-control study of both mild and severe SIM in Caucasian participants. Experiments elucidating the potential mechanism between *GATM* and SIM are

necessary to determine the specific conditions, if any, under which *GATM* may truly affect SIM.

Experimental Procedures

Participants

Cases and controls (n = 836) were derived from six medical centers in six states and provinces in the United States and in Canada representative of no single geographic location. Data for all participants was collected via a standardized questionnaire administered by a research coordinator. The Principal Investigator, Dr. Vladutiu, reviewed every questionnaire and individually telephoned every case that had gaps of information or inconsistencies. (This communication was documented). We have previously reported our definition of mild versus severe SIM (Vladutiu et al., 2011). Briefly, mildly affected cases were defined as participants with muscle aches and pains associated with the initiation of statin therapy that were reversible with cessation of therapy. Severely affected cases experienced symptoms of incapacitating muscle pain with or without weakness or with weakness alone that led to rhabdomyolysis in a number of cases and serum $CK > 4 \times ULN$ in 50% of cases in which it was quantified. Approximately 79% of participants continued to have severe symptoms for 6 months following discontinuation of statin therapy and 24% experienced progressive worsening with time. The time of onset of symptoms may have varied, but the association with statin therapy must have been clear to the referring physician and the participants themselves. Age- and gender-matched controls were recruited at collaborating centers following at least six months of statin therapy without myopathic symptoms. They were also monitored, via questionnaire, for change in status at 12 months. Details on the data collection and co-medication classifications can be found in the Supplemental Experimental Procedures. The study was approved by the institutional review boards at each study site, and all participants provided written informed consent.

Genotyping

Genomic DNA was prepared from whole blood collected in EDTA tubes with Gentra Puregene DNA isolation kits (Qiagen, Valencia, CA, USA). Genotypes for *GATM* rs9806699 were obtained using a TaqMan genotyping assay (C_30104701_10; Life Technologies, NY, USA) and analyzed with a MJR Opticon 2 real-time detection system (Bio-Rad, Hercules, CA, USA).

Statistical methods

Continuous variables were summarized as median and interquartile range and compared using the Kruskal Wallis test. Categorical variables were summarized as counts and percentages and compared using chi-squared or Fisher's exact test where necessary. The Monte Carlo estimate of the exact p-value for Hardy-Weinberg equilibrium (HWE) was calculated in the Caucasian subjects using 10,000 permutations. Genetic associations were evaluated by both allele- and genotype-based tests. The primary analysis was for the association with any SIM (mild or severe), and the secondary analyses assessed the associations with mild SIM alone and severe SIM alone. Univariate and age- and sexadjusted logistic regression models were used. Sensitivity analyses were performed in a sub-

group of participants (n = 386) without potentially confounding co-medications (defined in Supplemental Experimental Procedures) and a propensity-matched dataset. The purpose of propensity-matching was to eliminate the known differences in the characteristics and sample sizes between the cases and controls. The propensity-matched dataset matched control subjects with SIM (mild or severe) subjects 1:1 using a greedy $8 \rightarrow 1$ matching algorithm (Parsons, 2004; Rosenbaum and Rubin, 1983; D'Agostino, 1998). Cases and controls were matched based on the significantly different characteristics in Table 1 (statin therapy, coronary artery disease, hypertension, smoking status, family history of heart disease, obesity, and co-medications that could treat SIM). A fixed-effect meta-analysis of all studies evaluating the association between rs9806699 and SIM (Table S2) was performed (Senn et al, 2011). Data excluding fibrate users (Mangravite et al [2013] Marshfield cohort and Floyd et al [2014]) and any potentially interacting medications (Luzum et al [2015]) was used, except for the data from Carr et al (2014) because concomitant medication information was not available. The 95% confidence intervals from the Carr et al (2014) study were also not available, and thus they were estimated using the standard error from our data (lowest standard error of all studies). All statistical analyses were performed using SAS version 9.3 (Cary, NC, USA). P < 0.05 was considered statistically significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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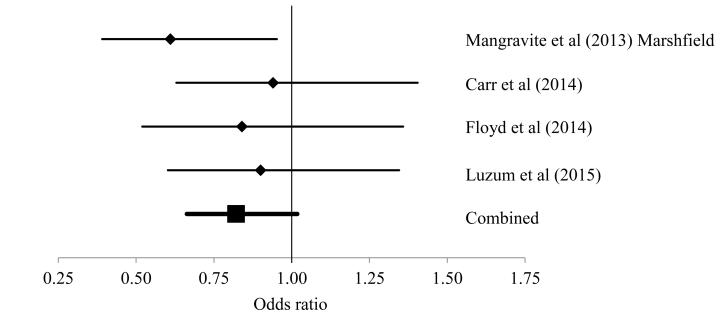


Figure 1.

Forest plot of odds ratios and 95% confidence intervals from individual studies of the association between *GATM* rs9806699 and SIM and the combined results from the fixed-effect meta-analysis. Data excluding fibrate users (Mangravite et al [2013] Marshfield cohort and Floyd et al [2014]) and any potentially interacting medications (Luzum et al [2015]) was used, except for the data from Carr et al (2014) because concomitant medication information was not available. The 95% confidence intervals from the Carr et al (2014) study were also not available, and thus they were estimated using the standard error from our data (lowest standard error of all studies).

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Table 1

Participant characteristics overall and stratified by GATM rs9806699 G>A genotype and SIM status.

AII AA AG A				Cases (n = 609; 85%)	(9)	Cor	Controls (n = 106; 15%)	(2%)	
374, (52%) $27, (51%)$ $134, (51%)$ $170, (66%)$ $quivalents (mg)$ $28, (1)$ $58, (15)$ $58, (15)$ $58, (15)$ $38, (11)$ $20, (10)$ $20, (10)$ $20, (10)$ $20, (10)$ $quivalents (mg)$ $20, (10)$ $20, (10)$ $20, (10)$ $20, (10)$ $143, (20%)$ $20, (50%)$ $144, (55%)$ $148, (49%)$ $143, (20%)$ $143, (20%)$ $24, (49%)$ $148, (49%)$ $143, (20%)$ $20, (10%)$ $20, (11%)$ $20, (13%)$ $143, (20%)$ $20, (10%)$ $20, (11%)$ $20, (13%)$ $143, (20%)$ $20, (10%)$ $20, (11%)$ $20, (13%)$ $143, (20%)$ $20, (10%)$ $20, (11%)$ $20, (11%)$ $153, (12%)$ $20, (11%)$ $20, (11%)$ $21, (11%)$ $153, (12%)$ $21, (11%)$ $21, (11%)$ $21, (11%)$ $154, (10%)$ $21, (11%)$ $21, (11%)$ $11, (11%)$ $110, (11, (10%))$ $21, (11%)$ $21, (11%)$ $11, (11%)$ $110, (11, (11, (11, (11, (11, (11, (11,$	Characteristic	All (n =715)	A/A (n = 43; 6%)		G/G (n = 305; 43%)	A/A (n = 7; 1%)	A/G (n = 41; 6%)	G/G (n = 58; 8%)	^a p-value
Sel (1)Sel (15)Sel (16)Sel (16)Sel (15)quivalents (mg) 20 (10) 20 (10) 20 (10) 20 (10) 20 (10) 32 (55%) 26 (60%) 144 (55%) 148 (49%) 20 (10) 143 (20%) 143 (20%) 26 (60%) 144 (55%) 148 (49%) 143 (20%) 143 (20%) 20 (11%) 20 (10) 20 (10) 143 (20%) 20 (11%) 20 (11%) 20 (11%) 20 (11%) 143 (20%) 20 (11%) 20 (11%) 20 (11%) 21 (38%) 143 (20%) 20 (30%) 21 (30%) 21 (30%) 21 (30%) 15 (20%) 20 (11%) 20 (30%) 21 (30%) 21 (30%) 15 (20%) 20 (30%) 21 (30%) 21 (30%) 21 (30%) 16 (20%) 21 (30%) 21 (30%) 21 (30%) 10 (30%) 10 (11%) 21 (30%) 21 (30%) 10 (30%) 10 (30%) 10 (11%) 21 (30%) 21 (30%) 10 (30%) 10 (30%) 10 (11%) 21 (30%) 21 (30%) 10 (30%) 10 (30%) 10 (11%) 21 (30%) 21 (30%) 10 (30%) 10 (30%) 10 (11%) 21 (30%) 21 (30%) 10 (30%) 10 (30%) 10 (11%) 21 (30%) 21 (30%) 10 (30%) 10 (30%) 10 (11%) 21 (30%) 21 (30%) 10 (30%) 10 (30%) 10 (11%) 21 (30%) 21 (30%) 10 (30%) 10 (30%) 10 (11%) 21 (30%) <td< td=""><td>Male gender</td><td>374 (52%)</td><td>22 (51%)</td><td>134 (51%)</td><td>170 (56%)</td><td>4 (57%)</td><td>18 (44%)</td><td>26 (46%)</td><td>0.615</td></td<>	Male gender	374 (52%)	22 (51%)	134 (51%)	170 (56%)	4 (57%)	18 (44%)	26 (46%)	0.615
quivalents (mg) 20 (10) 20 (10) 20 (10) 20 (10) quivalents (mg) 392 (55%) 26 (60%) 143 (55%) 148 (49%) 392 (55%) 26 (60%) 143 (55%) 148 (49%) 75 (55%) 40 (10) 37 (20%) 27 (20%) 27 (55%) 24 (39%) 52 (7%) 1 (25%) 20 (19%) 24 (39%) 24 (39%) 52 (7%) 1 (25%) 2 (39%) 24 (39%) 24 (39%) ase 1 37 (19%) 8 (19%) 24 (39%) 24 (39%) ase 1 37 (19%) 8 (19%) 24 (39%) 24 (39%) ase 1 37 (19%) 8 (19%) 24 (39%) 24 (39%) ase 1 37 (19%) 8 (19%) 14 (49%) 24 (39%) ase 1 37 (19%) 8 (19%) 13 (50%) 24 (39%) ase 1 34 (49%) 13 (50%) 14 (49%) 24 (39%) ase 1 34 (39%) 1 34 (39%) 13 (45%) 24 (39%) ase 1 34 (39%) 1 34 (39%) 1 (40%) <t< td=""><td>Age (years)</td><td>58 (11)</td><td>58 (15)</td><td>58 (16)</td><td>58 (15)</td><td>64 (13)</td><td>61 (13)</td><td>60 (17)</td><td>0.686</td></t<>	Age (years)	58 (11)	58 (15)	58 (16)	58 (15)	64 (13)	61 (13)	60 (17)	0.686
32 (55%) $26 (60%)$ $144 (55%)$ $148 (49%)$ $143 (20%)$ $133 (12%)$ $25 (27%)$ $75 (25%)$ $123 (12%)$ $10 (23%)$ $29 (11%)$ $39 (13%)$ $124 (12%)$ $20 (10%)$ $21 (3%)$ $24 (3%)$ $127 (12%)$ $10 (25%)$ $20 (8%)$ $24 (8%)$ $127 (12%)$ $10 (25%)$ $10 (25%)$ $24 (8%)$ $127 (19%)$ $10 (0%)$ $11 (4%)$ $13 (4%)$ $127 (19%)$ $17 (2%)$ $20 (8%)$ $24 (8%)$ $127 (19%)$ $137 (19%)$ $8 (19%)$ $6 (2%)$ $127 (19%)$ $137 (19%)$ $11 (4%)$ $13 (4%)$ $127 (19%)$ $137 (19%)$ $11 (4%)$ $13 (4%)$ $127 (19%)$ $137 (19%)$ $12 (16%)$ $41 (16%)$ $127 (19%)$ $137 (19%)$ $12 (16%)$ $12 (16%)$ $111 (16)$ $12 (16%)$ $12 (16%)$ $12 (16%)$ $111 (16)$ $12 (16%)$ $12 (16%)$ $12 (16%)$ $111 (16)$ $12 (16%)$ $12 (16%)$ $12 (16%)$ $111 (16)$ $12 (16%)$ $12 (16%)$ $11 (16%)$ $111 (16)$ $11 (16%)$ $11 (16%)$ $11 (16%)$ $111 (16)$ $11 (16%)$ $11 (16%)$ $11 (16%)$ $111 (16)$ $11 (16%)$ $11 (16%)$ $11 (16%)$ $111 (16)$ $11 (16%)$ $11 (16%)$ $11 (16%)$ $111 (16)$ $11 (16%)$ $11 (16%)$ $11 (16%)$ $111 (16)$ $11 (16%)$ $11 (16%)$ $11 (16%)$ $111 (16)$ $11 (12%)$ $11 (16%)$ $11 (16%)$	bAtorvastatin dose equivalents (mg)	20 (10)	20 (30)	10 (30)	20 (10)	15 (30)	10 (20)	10 (10)	0.374
(14)(14)(53, (20%))(57, (25%)) $(12, (10, (10)))$ $(10, (23, (10)))$ $(20, (11))$ $(20, (11))$ $(12, (11))$ $(12, (11))$ $(12, (11))$ $(12, (11))$ $(12, (11))$ $(12, (11))$ $(12, (11))$ $(12, (11))$ $(12, (11))$ $(12, (11))$ $(12, (12))$ $(12$	Atorvastatin	392 (55%)	26 (60%)	144 (55%)	148 (49%)	4 (57%)	27 (66%)	43 (74%)	0.006
83 (12%)10 (23%)29 (11%)39 (13%) $52 (7\%)$ 12% $20 (8\%)$ $3 (13\%)$ $3 (13\%)$ $52 (7\%)$ 12% $20 (8\%)$ $24 (8\%)$ $24 (8\%)$ $10 (10)$ $10 (10)$ $11 (4\%)$ $13 (4\%)$ $13 (4\%)$ $10 (10)$ $15 (2\%)$ $2 (5\%)$ $2 (5\%)$ $6 (2\%)$ $10 (10)$ $15 (2\%)$ $2 (5\%)$ $6 (2\%)$ $6 (2\%)$ $10 (10)$ $13 (10\%)$ $8 (19\%)$ $5 (12\%)$ $6 (2\%)$ $10 (10)$ $13 (10\%)$ $8 (19\%)$ $2 (14\%)$ $6 (14\%)$ $4 (14\%)$ $10 (10)$ $13 (10\%)$ $10 (10\%)$ $13 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (2\%)$ $10 (2\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (2\%)$ $10 (2\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (2\%)$ $10 (2\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (2\%)$ $10 (2\%)$ $10 (10\%)$ $10 (10\%)$ $10 (10)$ $10 (2\%)$ $10 (2\%)$ $10 (2\%)$ $10 (2\%)$ $10 (10)$ $10 (2\%)$ $10 (2\%)$ $10 (2\%)$ $10 (2\%)$ $10 (10)$ $10 (2\%)$ <t< td=""><td>Simvastatin</td><td>143 (20%)</td><td>4 (9%)</td><td>53 (20%)</td><td>75 (25%)</td><td>2 (29%)</td><td>6 (15%)</td><td>3 (5%)</td><td></td></t<>	Simvastatin	143 (20%)	4 (9%)	53 (20%)	75 (25%)	2 (29%)	6 (15%)	3 (5%)	
52 (7%) $1 (2%)$ $20 (8%)$ $24 (8%)$ $10 (4%)$ $30 (4%)$ $0 (0%)$ $11 (4%)$ $24 (8%)$ $10 (4%)$ $30 (4%)$ $0 (0%)$ $11 (4%)$ $13 (4%)$ $10 (4%)$ $15 (2%)$ $0 (0%)$ $11 (4%)$ $6 (2%)$ $10 (4, 10)$ $15 (2%)$ $8 (19%)$ $8 (19%)$ $6 (2%)$ $10 (15%)$ $8 (19%)$ $8 (19%)$ $8 (19%)$ $6 (2%)$ $10 (10, 10)$ $137 (19%)$ $8 (19%)$ $8 (19%)$ $6 (2%)$ $10 (10, 10)$ $137 (19%)$ $8 (19%)$ $8 (19%)$ $14 (14%)$ $10 (10, 10)$ $138 (47%)$ $10 (19%)$ $10 (10, 10)$ $10 (10, 10)$ $138 (47%)$ $10 (40%)$ $10 (40%)$ $10 (40%)$ $10 (10, 10)$ $338 (47%)$ $24 (5%)$ $10 (40%)$ $10 (40%)$ $10 (10, 10)$ $338 (47%)$ $24 (5%)$ $10 (40%)$ $10 (40%)$ $10 (10, 10)$ $338 (47%)$ $24 (5%)$ $10 (40%)$ $10 (4%)$ $10 (10, 10)$ $10 (40%)$ $10 (40%)$ $10 (4%)$ $10 (4%)$ $10 (10, 10)$ $10 (40%)$ $10 (40%)$ $10 (4%)$ $10 (4%)$ $10 (10, 10)$ $37%$ $37%$ $27%$ $10 (4%)$ $10 (4%)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10%)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10%)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10, 10)$ $10 (10, 10)$ 10	Rosuvastatin	83 (12%)	10 (23%)	29 (11%)	39 (13%)	0 (0%)	2 (5%)	3 (5%)	
30(4%) $10(%)$ $11(4%)$ $13(4%)$ $15(2%)$ $15(2%)$ $2(5%)$ $4(2%)$ $6(2%)$ n $15(2%)$ $2(5%)$ $4(2%)$ $6(2%)$ n $137(19%)$ $8(19%)$ $8(19%)$ $6(2%)$ n $97(14%)$ $8(19%)$ $8(19%)$ $44(14%)$ n $109(15%)$ $8(19%)$ $41(16%)$ $48(16%)$ n $109(15%)$ $8(19%)$ $130(50%)$ $154(5%)$ n $109(15%)$ $8(19%)$ $130(50%)$ $154(5%)$ n $109(15%)$ $24(5%)$ $104(40%)$ $103(34%)$ n $109(15%)$ $24(5%)$ $100(40%)$ $103(34%)$ n $109(15%)$ $24(5%)$ $100(40%)$ $103(34%)$ n $100(15%)$ $21(49%)$ $100(19%)$ $100(19%)$ n $100(13%)$ $21(49%)$ $100(19%)$ $100(19%)$ n $100(13%)$ $21(49%)$ $100(19%)$ $10(13%)$ n $100(13%)$ $21(19%)$ $21(10%)$ $21(10%)$ n $100(10%)$ $110(10%)$ $21(10%)$ $21(10%)$ n $100%$ $100%$ $100%$ $100%$ $21(10%)$ n $100%$ $100%$ $100%$ $21(10%)$ $21(10%)$ n $100%$ $100%$ $100%$ $21(10%)$ <	Pravastatin	52 (7%)	1 (2%)	20 (8%)	24 (8%)	0 (0%)	2 (5%)	5 (9%)	
15 (2%) $15 (2%)$ $1 (2%)$ $6 (2%)$ ase $137 (19%)$ $8 (19%)$ $57 (22%)$ $6 (2%)$ n $97 (14%)$ $8 (19%)$ $57 (25%)$ $64 (21%)$ n $97 (14%)$ $8 (19%)$ $8 (19%)$ $44 (14%)$ n $109 (15%)$ $8 (19%)$ $8 (19%)$ $44 (16%)$ n $109 (15%)$ $8 (19%)$ $10 (16%)$ $48 (16%)$ n $109 (15%)$ $8 (19%)$ $10 (10%)$ $10 (10%)$ n $109 (15%)$ $24 (5%)$ $10 (40%)$ $10 (3%)$ n $109 (15%)$ $24 (5%)$ $10 (40%)$ $10 (3%)$ n $10 (10%)$ $24 (5%)$ $10 (40%)$ $10 (3%)$ n $10 (10%)$ $24 (5%)$ $10 (40%)$ $10 (3%)$ scale $24 (5%)$ $21 (49%)$ $10 (40%)$ $10 (3%)$ scale $10 (10%)$ $21 (9%)$ $10 (40%)$ $10 (40%)$ scale $10 (10%)$ $21 (9%)$ $10 (3%)$ $10 (3%)$ scale $10 (13%)$ $21 (49%)$ $10 (40%)$ $10 (3%)$ scale $10 (3%)$ $21 (9%)$ $10 (3%)$ $10 (3%)$ scale $10 (3%)$ $21 (9%)$ $10 (3%)$ $10 (3%)$ scale $10 (3%)$ $21 (9%)$ $21 (9%)$ $10 (9%)$ scale $10 (3%)$ $21 (9%)$ $21 (9%)$ $10 (9%)$ scale $10 (3%)$ $21 (9%)$ $21 (9%)$ $21 (9%)$ scale $10 (3%)$ $21 (9%)$ $21 (9%)$ $21 (9%)$ scale $21 (9%)$ $21 (9%)$	Lovastatin	30 (4%)	0 (0%)	11 (4%)	13 (4%)	0 (0%)	4 (10%)	2 (3%)	
ase $137(19\%)$ $8(19\%)$ $57(22\%)$ $6(21\%)$ n $97(14\%)$ $97(14\%)$ $6(14\%)$ $39(15\%)$ $44(14\%)$ n $97(14\%)$ $8(19\%)$ $19(16\%)$ $48(16\%)$ $109(15\%)$ $8(19\%)$ $8(19\%)$ $11(16\%)$ $48(16\%)$ $109(15\%)$ $24(54\%)$ $24(56\%)$ $130(50\%)$ $154(50\%)$ $109(12\%)$ $245(34\%)$ $19(44\%)$ $104(40\%)$ $103(34\%)$ 11 disease $338(47\%)$ $24(54\%)$ $104(40\%)$ $103(34\%)$ 11 disease $345(48\%)$ $21(49\%)$ $104(40\%)$ $104(5\%)$ 100 disease $345(48\%)$ $21(49\%)$ $104(40\%)$ $104(5\%)$ 100 disease $345(48\%)$ $21(49\%)$ $104(40\%)$ $104(5\%)$ 100 disease $345(8\%)$ $21(49\%)$ $104(40\%)$ $104(5\%)$ 100 disease $21(3\%)$ $21(3\%)$ $21(3\%)$ $104(5\%)$ 100 disease $25(9\%)$ $21(9\%)$ $21(9\%)$ $21(9\%)$ 100 disease $21(9\%)$ $21(9\%)$ $21(9\%)$ $21(9\%)$ 100 disease $21(7\%)$ $21(9\%)$ $21(9\%)$ $21(9\%)$ 1000 disease $21(7\%)$ $21(9\%)$ $21(9\%)$ $21(9\%)$	Other statin	15 (2%)	2 (5%)	4 (2%)	6 (2%)	1 (14%)	(%0) 0	2 (3%)	
n $97(14\%)$ $6(14\%)$ $39(15\%)$ $41(16\%)$ $109(15\%)$ $109(15\%)$ $8(19\%)$ $41(16\%)$ $48(16\%)$ $107(1-2)$ $338(47\%)$ $24(56\%)$ $130(50\%)$ $134(50\%)$ $107(1-2)$ $338(47\%)$ $24(56\%)$ $130(50\%)$ $154(50\%)$ $107(1-2)$ $245(34\%)$ $19(44\%)$ $104(40\%)$ $103(34\%)$ $107(1-2)$ $245(34\%)$ $19(49\%)$ $104(40\%)$ $103(34\%)$ $107(1-2)$ $345(48\%)$ $21(49\%)$ $104(40\%)$ $103(34\%)$ $107(1-2)$ $245(34\%)$ $102(49\%)$ $103(34\%)$ $103(34\%)$ $107(1-2)$ $245(48\%)$ $102(49\%)$ $103(34\%)$ $103(34\%)$ $107(1-2)$ $245(48\%)$ $102(49\%)$ $103(34\%)$ $103(34\%)$ $107(1-2)$ $24(19\%)$ $102(19\%)$ $103(34\%)$ $103(34\%)$ $107(1-2)$ $21(19\%)$ $102(19\%)$ $103(19\%)$ $103(19\%)$ $107(1-2)$ $21(19\%)$ $21(19\%)$ $21(19\%)$ $21(19\%)$ $21(19\%)$ $107(1-2)$ $112(2\%)$ $112(10\%)$ $11(16\%)$ $21(19\%)$ $21(19\%)$ $107(1-2)$ $112(2\%)$ $112(19\%)$ $21(19\%)$ $21(19\%)$ $21(19\%)$ $107(1-2)$ $112(10\%)$ $112(10\%)$ $21(10\%)$ $21(19\%)$ $21(19\%)$ $107(1-2)$ $112(10\%)$ $112(10\%)$ $21(19\%)$ $21(19\%)$ $21(19\%)$ $107(1-2)$ $112(1-2)$ $112(1-2)$ $11(1-2)$ $21(10\%)$ $21(19\%)$ $107(1-2)$ $112(1-2)$ $112(1-2)$ $112(1-2)$ $112(1-2)$ <td>Coronary artery disease</td> <td>137 (19%)</td> <td>8 (19%)</td> <td>57 (22%)</td> <td>64 (21%)</td> <td>1 (14%)</td> <td>3 (7%)</td> <td>4 (7%)</td> <td>0.045</td>	Coronary artery disease	137 (19%)	8 (19%)	57 (22%)	64 (21%)	1 (14%)	3 (7%)	4 (7%)	0.045
109(15%) $8(19%)$ $41(16%)$ $48(16%)$ $120(12)$ $338(47%)$ $24(56%)$ $130(50%)$ $154(50%)$ $120(12)$ $245(4%)$ $12(49%)$ $12(45%)$ $124(50%)$ $110(12)$ $245(4%)$ $19(44%)$ $104(40%)$ $103(34%)$ $110(12)$ $245(4%)$ $21(49%)$ $104(40%)$ $103(34%)$ $120(12)$ $345(4%)$ $21(49%)$ $104(40%)$ $103(34%)$ $110(12)$ $245(4%)$ $21(49%)$ $104(40%)$ $103(34%)$ $120(12)$ $245(4%)$ $10(40%)$ $103(34%)$ $103(34%)$ $120(12)$ $21(49%)$ $18(7%)$ $103(34%)$ $103(34%)$ $120(12)$ $21(49%)$ $21(49%)$ $10(40%)$ $10(4%)$ $120(12)$ $21(49%)$ $21(49%)$ $2(10%)$ $2(9%)$ $110(12)$ $21(10)$ $21(10%)$ $21(10%)$ $21(10%)$ $110(12)$ $11(25%)$ $21(10%)$ $21(19%)$ $21(19%)$ $110(12)$ $11(2%)$ $11(12%)$ $21(19%)$ $21(19%)$ $110(12)$ $11(2%)$ $11(10%)$ $21(19%)$ $21(19%)$ $110(12)$ $11(2%)$ $11(10%)$ $21(10%)$ $21(10%)$ $110(12)$ $11(12%)$ $11(10%)$ $21(10%)$ $21(10%)$ $110(12)$ $11(10%)$ $11(10%)$ $21(10%)$ $21(10%)$ $110(12)$ $11(12%)$ $11(10%)$ $21(10%)$ $21(10%)$ $110(12)$ $11(12%)$ $11(12%)$ $21(10%)$ $21(10%)$ $110(12)$ $11(12%)$ $11(12%)$ $11(10$	Myocardial infarction	97 (14%)	6 (14%)	39 (15%)	44 (14%)	2 (29%)	5 (12%)	2 (3%)	0.219
338(47%) $24(56%)$ $130(50%)$ $154(50%)$ $110(10)$ $245(34%)$ $19(44%)$ $103(34%)$ $103(34%)$ $110(10)$ $245(34%)$ $19(44%)$ $103(34%)$ $103(34%)$ $110(10)$ $345(48%)$ $21(49%)$ $103(34%)$ $103(34%)$ $110(10)$ $345(48%)$ $21(49%)$ $138(53%)$ $104(54%)$ $110(10)$ $345(48%)$ $21(49%)$ $103(34%)$ $103(34%)$ $110(10)$ $12(6%)$ $21(49%)$ $103(34%)$ $103(34%)$ $110(10)$ $19(3%)$ $21(49%)$ $10(3%)$ $10(3%)$ $110(10)$ $25(8%)$ $3(7%)$ $25(10%)$ $10(13%)$ $110(10)$ $27(%)$ $27(%)$ $26(9%)$ $26(9%)$ $110(10)$ $11(2%)$ $27(10)$ $26(9%)$ $26(9%)$ $110(10)$ $11(2%)$ $27(10)$ $21(13%)$ $26(9%)$ $110(10)$ $11(2%)$ $21(10)$ $21(19%)$ $21(19%)$ $110(10)$ $11(2%)$ $11(2%)$ $21(19%)$ $21(19%)$ $110(10)$ $11(2%)$ $11(2%)$ $21(10%)$ $21(10%)$ $110(10)$ $11(2%)$ $11(2%)$ $21(10%)$ $21(19%)$ $110(10)$ $11(2%)$ $11(2%)$ $21(10%)$ $21(10%)$ $110(10)$ $11(10%)$ $11(10%)$ $21(10%)$ $21(10%)$ $110(10)$ $11(10)$ $11(10)$ $21(10)$ $21(10)$ $110(10)$ $11(10)$ $11(10)$ $21(10)$ $21(10)$ $110(10)$ $11(10)$ $11(10)$ $21(10)$ $21(10)$ <td>Diabetes</td> <td>109 (15%)</td> <td>8 (19%)</td> <td>41 (16%)</td> <td>48 (16%)</td> <td>2 (29%)</td> <td>4 (10%)</td> <td>6 (10%)</td> <td>0.628</td>	Diabetes	109 (15%)	8 (19%)	41 (16%)	48 (16%)	2 (29%)	4 (10%)	6 (10%)	0.628
$245 (34\%)$ $19 (44\%)$ $103 (34\%)$ $\operatorname{trdisease}$ $345 (48\%)$ $19 (40\%)$ $103 (34\%)$ $\operatorname{trdisease}$ $345 (48\%)$ $21 (49\%)$ $18 (7\%)$ $164 (54\%)$ scle $42 (6\%)$ $4 (9\%)$ $18 (7\%)$ $16 (5\%)$ scle $19 (3\%)$ $3 (7\%)$ $5 (2\%)$ $11 (4\%)$ scle $5 (8\%)$ $3 (7\%)$ $5 (2\%)$ $11 (4\%)$ scle $55 (8\%)$ $3 (7\%)$ $25 (10\%)$ $26 (9\%)$ scle $55 (8\%)$ $3 (7\%)$ $25 (10\%)$ $26 (9\%)$ scle $17 (3\%)$ $3 (7\%)$ $25 (10\%)$ $26 (9\%)$ mption $17 (2\%)$ $3 (7\%)$ $25 (10\%)$ $26 (9\%)$ mption $17 (2\%)$ $1 (2\%)$ $8 (3\%)$ $8 (3\%)$ mption $17 (2\%)$ $1 (2\%)$ $21 (16\%)$ $26 (10\%)$ mption $17 (2\%)$ $1 (2\%)$ $21 (10\%)$ $26 (10\%)$ mption $17 (2\%)$ $1 (2\%)$ $21 (10\%)$ $26 (2\%)$ mption $17 (2\%)$ $1 (2\%)$ $21 (10\%)$ $26 (2\%)$ mption $17 (2\%)$ $1 (2\%)$ $21 (3\%)$ $21 (3\%)$ mption $17 (2\%)$ $1 (2\%)$ $21 (3\%)$ $21 (3\%)$ mption $1 (2\%)$ $1 (2\%)$ $21 (3\%)$ $21 (3\%)$ mption $1 (2\%)$ $1 (2\%)$ $21 (3\%)$ $21 (3\%)$ mption $1 (2\%)$ $1 (2\%)$ $21 (3\%)$ $21 (3\%)$ mption $1 (2\%)$ $1 (2\%)$ $21 (3\%)$ <td< td=""><td>Hypertension</td><td>338 (47%)</td><td>24 (56%)</td><td>130 (50%)</td><td>154 (50%)</td><td>2 (29%)</td><td>10 (24%)</td><td>17 (29%)</td><td>0.001</td></td<>	Hypertension	338 (47%)	24 (56%)	130 (50%)	154 (50%)	2 (29%)	10 (24%)	17 (29%)	0.001
Int disease $345 (48\%)$ $21 (49\%)$ $138 (53\%)$ $164 (54\%)$ sicle disease $42 (6\%)$ $4 (9\%)$ $18 (7\%)$ $16 (5\%)$ scale $19 (3\%)$ $3 (7\%)$ $2 (7\%)$ $16 (5\%)$ case $19 (3\%)$ $3 (7\%)$ $5 (2\%)$ $11 (4\%)$ c disease $55 (8\%)$ $3 (7\%)$ $2 (10\%)$ $2 (9\%)$ c disease $19 (13\%)$ $3 (7\%)$ $2 (10\%)$ $2 (9\%)$ mption $17 (2\%)$ $3 (7\%)$ $2 (10\%)$ $2 (9\%)$ mption $17 (2\%)$ $1 (2\%)$ $8 (3\%)$ $8 (3\%)$ mption $17 (2\%)$ $1 (2\%)$ $2 (10\%)$ $5 (10\%)$ mption $17 (2\%)$ $1 (2\%)$ $2 (10\%)$ $5 (2\%)$ mption $17 (2\%)$ $1 (2\%)$ $2 (10\%)$ $5 (2\%)$ mption $17 (2\%)$ $1 (2\%)$ $2 (10\%)$ $5 (2\%)$	Smoker	245 (34%)	19 (44%)	104 (40%)	103 (34%)	2 (29%)	7 (17%)	9 (16%)	0.001
scle disease $42 (6\%)$ $4 (9\%)$ $18 (7\%)$ $16 (5\%)$ ease $19 (3\%)$ $3 (7\%)$ $5 (2\%)$ $11 (4\%)$ case $5 (3\%)$ $3 (7\%)$ $5 (2\%)$ $11 (4\%)$ c disease $5 (8\%)$ $3 (7\%)$ $2 (9\%)$ $2 (9\%)$ c disease $5 (3\%)$ $3 (7\%)$ $2 (10\%)$ $2 (9\%)$ mption $17 (2\%)$ $1 (2\%)$ $8 (3\%)$ $8 (3\%)$ mption $17 (2\%)$ $1 (2\%)$ $8 (3\%)$ $8 (3\%)$ mption $17 (2\%)$ $1 (2\%)$ $5 (20\%)$ $5 (18\%)$ mption $1 (2\%)$ $0 (0\%)$ $1 (4\%)$ $6 (2\%)$ mption $1 (2\%)$ $1 (2\%)$ $2 (18\%)$ $5 (18\%)$ mption $1 (2\%)$ $1 (2\%)$ $5 (20\%)$ $5 (2\%)$	Family history of heart disease	345 (48%)	21 (49%)	138 (53%)	164 (54%)	3 (43%)	9 (22%)	10 (17%)	< .001
scase $19(3\%)$ $3(7\%)$ $5(2\%)$ $11(4\%)$ c disease $55(8\%)$ $3(7\%)$ $25(10\%)$ $26(9\%)$ c disease $57(8\%)$ $3(7\%)$ $26(9\%)$ $26(9\%)$ mption $17(2\%)$ $3(7\%)$ $41(16\%)$ $40(13\%)$ mption $17(2\%)$ $1(2\%)$ $8(3\%)$ $8(3\%)$ mption $17(2\%)$ $1(2\%)$ $8(3\%)$ $8(3\%)$ mption $17(2\%)$ $11(26\%)$ $52(20\%)$ $54(18\%)$ mption $17(2\%)$ $0(0\%)$ $11(4\%)$ $6(2\%)$ mption $12(2\%)$ $1(2\%)$ $52(20\%)$ $54(18\%)$ mption $17(2\%)$ 100% $11(4\%)$ $5(2\%)$ mption $12(2\%)$ 100% $11(4\%)$ $5(2\%)$ mption $11(2\%)$ 12% 100% $51(10\%)$ mption $11(2\%)$ 100% $11(4\%)$ $5(2\%)$	Family history of muscle disease	42 (6%)	4 (9%)	18 (7%)	16 (5%)	0 (0%)	1 (2%)	3 (5%)	0.758
c disease 55 (8%) 3 (7%) 25 (10%) 26 (9%) c disease 91 (13%) 3 (7%) 41 (16%) 40 (13%)mption 17 (2%) 12 (12%) 8 (3%) 8 (3%) c mption 17 (2%) $1(26)$ 8 (3%) 8 (3%) c mption 17 (2%) $1(26)$ 52 (20%) 54 (18%) c mption 17 (2%) 0 (0%) 11 (4%) 6 (2%) c mption 17 (2%) 122 (17%) 122 (17%) 52 (20%) 54 (18%)	Metabolic muscle disease	19 (3%)	3 (7%)	5 (2%)	11 (4%)	0 (0%)	0 (0%)	0 (0%)	0.217
mption $91(13\%)$ $3(7\%)$ $41(16\%)$ $40(13\%)$ mption $17(2\%)$ $1(2\%)$ $8(3\%)$ $8(3\%)$ $17(2\%)$ $1(2\%)$ $8(3\%)$ $8(3\%)$ $8(3\%)$ $17(2\%)$ $11(26\%)$ $52(20\%)$ $54(18\%)$ $17(2\%)$ 00% $11(4\%)$ $6(2\%)$ $14(2\%)$ $1(2\%)$ $7(3\%)$ $5(2\%)$	Inflammatory muscle disease	55 (8%)	3 (7%)	25 (10%)	26 (9%)	0 (0%)	0 (0%)	1 (2%)	0.114
mption $17(2\%)$ $1(2\%)$ $8(3\%)$ $8(3\%)$ $122(17\%)$ $11(26\%)$ $52(20\%)$ $54(18\%)$ $17(2\%)$ $0(0\%)$ $11(4\%)$ $6(2\%)$ $14(2\%)$ $1(2\%)$ $7(3\%)$ $5(2\%)$	Hypothyroidism	91 (13%)	3 (7%)	41 (16%)	40 (13%)	0(0%)	3 (7%)	4 (7%)	0.200
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	Heavy alcohol consumption	17 (2%)	1 (2%)	8 (3%)	8 (3%)	0 (0%)	0 (0%)	0 (0%)	0.768
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	Obesity	122 (17%)	11 (26%)	52 (20%)	54 (18%)	0 (0%)	3 (7%)	2 (3%)	0.008
14 (2%) 1 (2%) 7 (3%) 5 (2%)	Liver disease	17 (2%)	0 (0%)	11 (4%)	6 (2%)	0 (0%)	0 (0%)	0 (0%)	0.326
	Kidney disease	14 (2%)	1 (2%)	7 (3%)	5 (2%)	0 (0%)	0 (0%)	1 (2%)	0.881
2 (5%) 13 (5%) 18 (6%)	ing	34 (5%)	2 (5%)	13 (5%)	18 (6%)	0 (0%)	1 (2%)	0 (0%)	0.480

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			Cases (n = 609; 85%)	%0)	Con	Controls $(n = 106; 15\%)$	5%)	
Characteristic	All $(n = 715)$	A/A (n = 43; 6%)	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	G/G (n = 305; 43%)	$\begin{array}{c c} A/A \\ (n=7;1\%) \end{array} A/G \\ (n=4;1\%) \end{array}$	A/G (n = 41; 6%)	G/G (n = 58; 8%)	<i>a</i> p-value
^c Participants taking 1 co-medication(s) that could treat SIM	260 (36%)	260 (36%) 21 (49%)	114 (44%)	109 (36%)	0 (0%)	7 (17%)	9 (16%)	<.001
^c Participants taking 1 co-medication(s) that could increase statin exposure	77 (11%) 7 (16%)	7 (16%)	31 (12%)	29 (10%)	(%0)0	3 (7%)	7 (12%)	0.665
^c Participants taking 1 co-medication(s) that could decrease statin exposure	7 (1%) 1 (2%)	1 (2%)	2 (1%)	2 (1%)	0 (0%)	1 (2%)	1 (2%)	0.333

^aContinuous variables are presented as median (interquartile range) and compared with the Kruskal-Wallis test. Categorical variables are presented as counts (%) and compared with the chi-square or Fisher's exact test where necessary. P-values are for the comparison of all groups stratified by GATM rs9806699 genotype and SIM status. Bolded values are for p < 0.05. b Atorvastatin dose equivalents were calculated as follows: fluvastatin dose/8, lovastatin dose/4, pravastatin dose/4, rosuvastatin dose*4, and simvastatin dose/2 (Stone et al., 2014). Dose equivalents were missing for cerivastatin (n = 6) and pitavastatin (n = 1).

^c Categories of potentially confounding co-medications are defined in the Supplemental Experimental Procedures section. GATM = gene encoding glycine amidinotransferase; SIM = statin-induced myopathy

Table 2

GATM rs9806699 minor allele and genotype frequencies in the controls, mild SIM cases, and severe SIM cases.

	All	subjects (n =	715)	
	Control (n = 106)	$ \begin{array}{l} \text{Mild SIM} \\ (n = 324) \end{array} $	Severe SIM (n = 285)	p-value
MAF (A)	0.26	0.28	0.29	0.447
A/A	0.07	0.08	0.06	0.436
G/A	0.39	0.40	0.47	
G/G	0.55	0.52	0.48	
Subject	s without cor	founding co-1	medications (n =	= 386)
	Control (n = 80)	Mild SIM (n = 165)	Severe SIM (n = 141)	p-value
MAF (A)	0.28	0.26	0.25	0.605
A/A	0.09	0.07	0.04	0.598
G/A	0.38	0.39	0.43	
G/G	0.54	0.55	0.54	
	Propensity-	matched datas	set (n = 188)	
	Control (n = 94)	Mild SIM (n = 44)	Severe SIM (n = 50)	p-value
MAF (A)	0.26	0.31	0.28	0.489
A/A	0.07	0.07	0.04	0.475
G/A	0.37	0.48	0.48	
G/G	0.55	0.45	0.48	

MAF = minor allele frequency; SIM = statin-induced myopathy

Table 3

Logistic regression modeling results

ModelOutcomeCovariatesOdds ratio 55% CT1control vs SIM (mild and severe)age + sex 1.17 $(0.78-1.17)$ 2control vs SIM (mild and severe)age + sex 1.11 $(0.79-1.58)$ 4control vs mild SIM onlynone 1.11 $(0.75-1.77)$ 5control vs mild SIM onlyage + sex 1.15 $(0.75-1.77)$ 6control vs mild SIM onlyage + sex 1.15 $(0.75-1.77)$ 7control vs severe SIM onlyage + sex 1.19 $(0.76-1.85)$ 7control vs severe SIM onlyage + sex 1.19 $(0.76-1.85)$ 7control vs severe SIM onlyage + sex 1.10 $(0.76-1.42)$ 8control vs severe SIM onlynone 0.90 $(0.61-1.42)$ 9control vs mild SIM onlyage + sex 1.00 $(0.61-1.42)$ 11control vs mild SIM onlynone 0.93 $(0.61-1.42)$ 12control vs mild SIM onlynone 0.93 $(0.61-1.42)$ 13control vs mild SIM onlynone 0.93 $(0.61-1.42)$ 14control vs mild SIM onlynone 0.93 $(0.61-1.42)$ 15control vs mild SIM onlynone 0.93 $(0.61-1.42)$ 16control vs mild SIM onlynone 0.93 $(0.61-1.42)$ 17control vs mild SIM onlynone 0.93 $(0.61-1.42)$ 18control vs mild SIM onlynone 0.93 $(0.61-1.42)$ 17control vs sever		All sub	All subjects (n = 715)			
control vs SIM (mild and severe)none1.14control vs SIM (mild and severe)age + sex1.17control vs mild SIM onlynone1.11control vs mild SIM onlyage + sex1.15control vs severe SIM onlyage + sex1.19control vs severe SIM onlyage + sex1.100control vs SIM (mild and severe)none0.901control vs SIM (mild and severe)age + sex1.000control vs severe SIM onlyage + sex1.000control vs severe SIM onlyage + sex0.91control vs severe SIM onlyage + sex1.33control vs severe SIM onlynone1.33control vs severe SIM onlynone1.13control vs severe SIM onlyage + sex1.13control vs severe SIM onlynone1.23control vs severe SIM onlyage + sex1.23control vs severe SIM onlyage + sex1.33control vs	Model	Outcome	Covariates	Odds ratio	95% CI	p-value
control vs SIM (mild and severe)age + sex1.17control vs mild SIM onlynone1.11control vs mild SIM onlyage + sex1.15control vs severe SIM onlyage + sex1.19control vs severe SIM onlyage + sex0.40control vs SIM (mild and severe)none0.90control vs SIM (mild and severe)none0.90control vs SIM (mild and severe)age + sex1.00control vs SIM (mild and severe)age + sex1.00control vs SIM (mild and severe)age + sex1.06control vs mild SIM onlynone0.93control vs mild SIM onlyage + sex1.06control vs severe SIM onlyage + sex1.06control vs severe SIM onlynone0.93control vs severe SIM onlyage + sex1.06control vs severe SIM onlyage + sex1.33control vs severe SIM onlyage + sex1.33control vs severe SIM onlynone1.33control vs mild SIM onlyage + sex1.33control vs severe SIM onlynone1.23control vs mild SIM onlynone1.23control vs mild SIM onlyage + sex1.33control vs severe SIM onlynone1.23control vs severe SIM onlynone1.23 <trr>control vs severe SIM only</trr>	1	control vs SIM (mild and severe)	anone	1.14	(0.82–1.61)	0.437
control vs mild SIM onlynone1.11control vs mild SIM onlyage + sex1.15control vs severe SIM onlynone1.18control vs severe SIM onlynone1.19control vs severe SIM onlyage + sex1.19control vs severe SIM onlyage + sex1.19Subjects without potentially confounding medications (n = 0.0000.000control vs SIM (mild and severe)age + sex0.000control vs SIM (mild and severe)age + sex1.000control vs mild SIM onlyage + sex0.901control vs severe SIM onlyage + sex0.91control vs severe SIM onlyage + sex1.13control vs severe SIM onlyage + sex1.33control vs severe SIM onlyage + sex1.30 <td>2</td> <td>control vs SIM (mild and severe)</td> <td>age + sex</td> <td>1.17</td> <td>(0.78–1.77)</td> <td>0.447</td>	2	control vs SIM (mild and severe)	age + sex	1.17	(0.78–1.77)	0.447
control vs mild SIM onlyage + sex1.15control vs severe SIM onlynone1.18control vs severe SIM onlyage + sex1.19control vs severe SIM onlyage + sex1.19Subjects without potentiallyCovariatesOdds ratioSubjects without potentiallyCovariates040outcomeCovariates040control vs SIM (mild and severe)age + sex1.00control vs SIM (mild and severe)age + sex1.00control vs SIM (mild and severe)age + sex1.00control vs mild SIM onlynone0.93control vs severe SIM onlyage + sex1.00control vs severe SIM onlyage + sex0.91control vs severe SIM onlyage + sex0.91control vs severe SIM onlyage + sex0.91control vs severe SIM onlyage + sex1.106control vs severe SIM onlyage + sex1.33control vs severe SIM onlyage + sex1.33control vs severe SIM onlyage + sex1.33control vs SIM (mild and severe)age + sex1.33control vs severe SIM onlyage + sex1.33c	4	control vs mild SIM only	anone	1.11	(0.79–1.58)	0.548
control vs severe SIM onlynone1.18control vs severe SIM onlyage + sex1.19Subjects without potentiallyage + sex1.19Subjects without potentiallyCovariatesOdds ratiocontrol vs SIM (mild and severe)covariates0.90control vs SIM (mild and severe)age + sex1.00control vs SIM (mild and severe)age + sex1.00control vs mild SIM onlynone0.93control vs mild SIM onlyage + sex1.06control vs severe SIM onlyage + sex0.91control vs severe SIM onlyage + sex1.19control vs severe SIM onlyage + sex1.33control vs severe SIM onlynone1.33control vs severe SIM onlynone1.33control vs sind SIM onlyage + sex1.33control vs severe SIM onlyage + sex1.33control vs severe SIM onlynone1.23control vs severe SIM onlynone1.33control vs severe SIM onlyage + sex1.70control vs severe SIM onlynone1.33control vs severe SIM onlynone1.33control vs severe SIM onlynone1.33 <trtr>control vs severe SIM o</trtr>	5	control vs mild SIM only	age + sex	1.15	(0.75–1.77)	0.517
control vs severe SIM onlyage + sex1.19Subjects without potentially confounding 1.10 Subjects without potentially confounding 0.90 CoutcomeCovariates 0.90 control vs SIM (mild and severe)age + sex 1.00 control vs SIM (mild and severe)age + sex 1.00 control vs mild SIM onlynone 0.93 control vs mild SIM onlyage + sex 1.00 control vs severe SIM onlyage + sex 0.91 control vs severe SIM onlyage + sex 1.19 control vs severe SIM onlyage + sex 1.33 control vs SIM (mild and severe)age + sex 1.33 control vs SIM (mild and severe)age + sex 1.33 control vs severe SIM onlyage + sex 1.70 control vs severe SIM onlyage + sex 1.70 control vs severe SIM onlyage + sex 1.77	9	control vs severe SIM only	anone	1.18	(0.81–1.72)	0.382
Subjects without potentially confounding medications (n =Subjects without potentially confounding medications (n =CovariatesOdds ratiocontrol vs SIM (mild and severe)age + sex0.90control vs NIM (mild and severe)age + sex1.00control vs mild SIM onlynone0.93control vs mild SIM onlyage + sex1.06control vs severe SIM onlyage + sex0.91control vs severe SIM onlyage + sex1.19control vs severe SIM onlyage + sex1.33control vs SIM (mild and severe)age + sex1.33control vs SIM (mild and severe)age + sex1.33control vs mild SIM onlynone1.23control vs mild SIM onlyage + sex1.70control vs severe SIM onlyage + sex1.70control vs severe SIM onlyage + sex1.06control vs severe SIM onlyage + sex1.77control vs severe SIM onlyage + sex1.17control vs severe SIM onlyage + sex1.17control vs severe SIM onlyage + sex1.17control vs severe SIM onlyage + sex1.17 </td <td>L</td> <td>control vs severe SIM only</td> <td>age + sex</td> <td>1.19</td> <td>(0.76 - 1.85)</td> <td>0.453</td>	L	control vs severe SIM only	age + sex	1.19	(0.76 - 1.85)	0.453
OutcomeCovariatesOdds ratiocontrol vs SIM (mild and severe)none 0.90 control vs SIM (mild and severe)age + sex 1.00 control vs mild SIM onlynone 0.93 control vs mild SIM onlyage + sex 1.00 control vs mild SIM onlyage + sex 1.06 control vs severe SIM onlyage + sex 0.93 control vs severe SIM onlyage + sex 0.91 control vs severe SIM onlyage + sex 1.19 control vs SIM (mild and severe)age + sex 1.33 control vs SIM (mild and severe)age + sex 1.33 control vs severe SIM onlynone 1.23 control vs severe SIM onlyage + sex 1.70 control vs severe SIM onlyage + sex 1.70 control vs severe SIM onlyage + sex 1.77		Subjects without potentially	confounding 1	medications (n		
control vs SIM (mild and severe)none 0.90 control vs SIM (mild and severe)age + sex 1.00 control vs mild SIM onlynone 0.93 control vs mild SIM onlyage + sex 1.06 control vs severe SIM onlyage + sex 0.91 control vs SIM (mild and severe)age + sex 1.33 control vs SIM (mild and severe)age + sex 1.33 control vs mild SIM onlynone 1.23 control vs mild SIM onlyage + sex 1.70 control vs severe SIM onlyage + sex 1.77	Model	Outcome	Covariates	Odds ratio	95% CI	p-value
control vs SIM (mild and severe)age + sex1.00control vs mild SIM onlynone 0.93 control vs mild SIM onlyage + sex 1.06 control vs severe SIM onlyage + sex 0.91 control vs SIM (mild and severe)covariates $0.46x$ ratiocontrol vs SIM (mild and severe)age + sex 1.33 control vs SIM (mild and severe)age + sex 1.23 control vs mild SIM onlynone 1.23 control vs severe SIM onlyage + sex 1.70 control vs severe SIM onlynone 1.08 control vs severe SIM onlyage + sex 1.70 control vs severe SIM onlyage + sex 1.77	8	control vs SIM (mild and severe)	anone	06.0	(0.60 - 1.34)	0.598
control vs mild SIM onlynone 0.93 control vs mild SIM onlyage + sex 1.06 control vs severe SIM onlyage + sex 0.91 control vs severe SIM onlyage + sex 0.91 control vs severe SIM onlyage + sex 0.91 Propensity-matched dataset 0.91 0.91 Propensity-matched dataset 0.91 0.91 control vs SIM (mild and severe)none 1.19 control vs SIM (mild and severe)age + sex 1.33 control vs SIM (mild and severe)age + sex 1.33 control vs SIM (mild and severe)age + sex 1.33 control vs SIM (mild and severe)age + sex 1.33 control vs smild SIM onlynone 1.33 control vs severe SIM onlyage + sex 1.70 control vs severe SIM onlynone 1.08 control vs severe SIM onlyage + sex 1.70	6	control vs SIM (mild and severe)	age + sex	1.00	(0.61 - 1.62)	0.982
control vs mild SIM onlyage + sex 1.06 control vs severe SIM onlynone 0.86 control vs severe SIM onlyage + sex 0.91 control vs severe SIM onlyage + sex 0.91 Propensity-matched dataset 1.19 1.19 control vs SIM (mild and severe)none 1.19 control vs SIM (mild and severe)age + sex 1.33 control vs SIM (mild and severe)age + sex 1.33 control vs SIM (mild and severe)age + sex 1.23 control vs mild SIM onlynone 1.23 control vs severe SIM onlyage + sex 1.70 control vs severe SIM onlynone 1.070 control vs severe SIM onlyage + sex 1.70	11	control vs mild SIM only	none	0.93	(0.61 - 1.42)	0.737
control vs severe SIM onlynone 0.86 control vs severe SIM only $age + sex$ 0.91 Forontrol vs severe SIM only $age + sex$ 0.91 Propensity-matched dataset 0.91 0.91 Propensity on the severe SIM only 0.96 0.70 Propensity on the severe SIM only 0.96 0.108 Propensity on the severe SIM only 0.96 0.117	12	control vs mild SIM only	age + sex	1.06	(0.63 - 1.77)	0.833
control vs severe SIM only age + sex 0.91 Propensity-matched dataset (n = 188) Propensity-matched dataset (n = 188) Outcome Covariates 0dds ratio control vs SIM (mild and severe) none 1.19 control vs SIM (mild and severe) age + sex 1.33 control vs SIM (mild and severe) age + sex 1.23 control vs mild SIM only none 1.23 control vs mild SIM only age + sex 1.70 control vs severe SIM only age + sex 1.70	13	control vs severe SIM only	none	0.86	(0.55 - 1.36)	0.523
Propensity-matched dataset (n = 188) Outcome Covariates 0dds ratio control vs SIM (mild and severe) none 1.19 control vs SIM (mild and severe) age + sex 1.33 control vs SIM (mild and severe) age + sex 1.33 control vs mild SIM only none 1.23 control vs mild SIM only age + sex 1.70 control vs severe SIM only age + sex 1.08 control vs severe SIM only age + sex 1.70	14	control vs severe SIM only	age + sex	0.91	(0.53 - 1.57)	0.740
OutcomeCovariatesOdds ratiocontrol vs SIM (mild and severe)none1.19control vs SIM (mild and severe)age + sex1.33control vs mild SIM onlynone1.23control vs mild SIM onlyage + sex1.70control vs severe SIM onlynone1.08control vs severe SIM onlyage + sex1.70		Propensity-ma	tched dataset (n = 188)		
control vs SIM (mild and severe)none1.19control vs SIM (mild and severe)age + sex1.33control vs mild SIM onlynone1.23control vs mild SIM onlyage + sex1.70control vs severe SIM onlynone1.08control vs severe SIM onlyage + sex1.08	Model	Outcome	Covariates	Odds ratio	95% CI	p-value
control vs SIM (mild and severe)age + sex1.33control vs mild SIM onlynone1.23control vs mild SIM onlyage + sex1.70control vs severe SIM onlynone1.08control vs severe SIM onlyage + sex1.17	15	control vs SIM (mild and severe)	none	1.19	(0.74 - 1.90)	0.475
control vs mild SIM onlynone1.23control vs mild SIM onlyage + sex1.70control vs severe SIM onlynone1.08control vs severe SIM onlyage + sex1.17	16	control vs SIM (mild and severe)	age + sex	1.33	(0.75–2.36)	0.338
control vs mild SIM only age + sex 1.70 control vs severe SIM only none 1.08 control vs severe SIM only age + sex 1.17	17	control vs mild SIM only	none	1.23	(0.70 - 2.16)	0.482
control vs severe SIM only none 1.08 control vs severe SIM only age + sex 1.17	18	control vs mild SIM only	age + sex	1.70	(0.80 - 3.60)	0.170
control vs severe SIM only age + sex 1.17	19	control vs severe SIM only	none	1.08	(0.61 - 1.88)	0.800
	20	control vs severe SIM only	age + sex	1.17	(0.60 - 2.28)	0.648

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CI = confidence interval; SIM = statin-induced myopathy