Association of Daily Dosage and Type of Statin Agent With Risk of Open-Angle Glaucoma

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Abstract

IMPORTANCE—There is growing evidence that statins may protect against the development or worsening of open-angle glaucoma (OAG). As researchers plan clinical trials to more definitively study whether statins indeed protect against OAG, it would be helpful to know whether specific daily dosages or types of statin confer a greater protective effect than others.

OBJECTIVE—To assess whether the protective effect of statins on the risk of glaucoma varies depending on the daily dosage or type of statin taken.

DESIGN, SETTING, AND PARTICIPANTS—Using claims data from January 2001 to December 2009, we observed 25 420 patients with no preexisting glaucoma and quantified exposure to statins and other cholesterol-lowering medications. Using multivariable regression modeling, we assessed the hazard of developing OAG and how it varied by the daily dosage or type of statin and whether any protective effect persists after accounting for baseline low-density lipoprotein level.

EXPOSURES—Different daily dosages and types of statins.

MAIN OUTCOMES AND MEASURES—Hazard ratios (HRs) for developing OAG with 95% CIs.

RESULTS—Of the 25 420 patients who met the eligibility criteria for study inclusion, the mean (SD) age was 66.1 (5.8) years, and 14 112 (55.5%) were female. Additionally, 19 232 patients (84.1%) were white, 1252 (5.5%) were black, and 1558 (6.8%) were Latino. After accounting for baseline low-density lipoprotein levels, persons who filled prescriptions for statins continuously for 2 years had a 21% reduced risk of glaucoma compared with nonusers (adjusted HR, 0.79; 95% CI, 0.66–0.96; *P* = .02). There was no additional protective effect associated with taking the highest dosage of statins (80 mg) compared with a lower dosage (40 mg) (HR, 1.03; 95% CI, 0.59–1.80; *P* = .91). The protective effect of the following statins on OAG risk did not differ compared with atorvastatin, an inexpensive generic statin: lovastatin (HR, 1.09; 95% CI, 0.71–1.68; *P* = .69), cerivastatin (HR, 0.61; 95% CI, 0.09–4.41; *P* = .63), rosuvastatin (HR, 0.83; 95% CI, 0.48–1.44; *P* = .51), fluvastatin (HR, 0.89; 95% CI, 0.39–2.02; *P* = .78), pravastatin (HR, 1.29; 95% CI, 0.93–1.79; *P* = .13), and simvastatin (HR, 1.03; 95% CI, 0.83–1.29; *P* = .78).

CONCLUSIONS AND RELEVANCE—Even after accounting for baseline low-density lipoprotein level, statin exposure continued to be associated with a reduction in OAG risk. Our study helps inform researchers of a reasonable daily dosage and type of statin to use when designing randomized clinical trials to assess the association between statin use and glaucoma.

Evidence suggests that statins may protect against open-angle glaucoma (OAG).[1–11] In 2012, we assessed the association between statins and OAG among more than 500000 managed-care enrollees with hyperlipidemia.[11] We found that persons with hyperlipidemia who took statins continuously for 2 years had an 8% decreased OAG risk relative to nonusers (*P* = .006) and a 9% decreased risk of progressing from glaucoma suspect to OAG compared with nonusers (*P* = .006).[11] While these findings support other studies demonstrating that statins may help protect against OAG,[1–10] the definitive means of assessing the role of statins in glaucoma care is to perform a randomized clinical trial (RCT). Before embarking on an RCT, there are additional questions that can be explored using claims data. Here, we use the same data source as our previous study[11] to assess whether (1) the apparent beneficial effect of statins on OAG risk is limited to persons with elevated low-density lipoprotein (LDL) cholesterol levels, (2) the use of a particular daily dosage of statin is required to achieve a beneficial effect, and (3) the use of a particular statin type protects best against OAG.

Methods

We used the Clinformatics Data Mart (OptumInsight), a claims database of enrollees in a nationwide managed-care network. To keep analyses consistent with our past work,[11] we used data from January 2001 to December 2009. This database captures ocular and nonocular diagnoses by using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*)[12] codes and contains information on enrollees' sociodemographic characteristics, outpatient prescriptions filled, and laboratory test results. All enrollees in the medical plan were also in the pharmacy plan. The University of Michigan Institutional Review Board approved this study, and because data were taken from a deidentified database, informed consent was waived.

We identified enrollees 60 years and older with hyperlipidemia (*ICD-9-CM* code 272.x) and no preexisting OAG diagnosis in the previous 2 years. Those with less than 2 years of plan enrollment, any noncontinuous enrollment, or no ophthalmologist or optometrist visits were excluded. Each enrollee had to have at least 1 LDL measurement within 6 months of the index date (2 years after plan enrollment). Multivariable Cox proportional hazards regression modeling assessed the hazard for developing OAG. We created 3 models. For each model, enrollees were observed from the index date until OAG onset or their last eye-care visit. The outcome of interest was diagnosis of OAG (*ICD-9-CM* codes 365.1, 365.10–12, and 365.15). Covariates included sociodemographic characteristics (age, sex, race/ethnicity, household net worth, education level, and region of residence), medical comorbidities (systemic hypotension, obesity, sleep apnea, migraine, diabetes, and hypertension), ocular comorbidities (cataract, pseudophakia/ aphakia, macular degeneration, and diabetic retinopathy), other cholesterol-lowering medication use, and Charlson Comorbidity Index score,[13] which measures disease burden. Additional methodological details appear elsewhere.[11]

All 3 models assessed the possible associations among the use of statins, use of other cholesterol-lowering drugs, and baseline LDL measurements and the hazard for OAG. Model 1 included statin use as a time-dependent variable. For every day after the index date, we calculated the number of days (later converted to months) each beneficiary received a statin over the previous 24 months. Model 2 assessed whether daily statin dosage was associated with the hazard for OAG. Here, we compared users who filled prescriptions for exclusively 10 mg, 20 mg, and 80 mg of statins daily with users of 40 mg daily. Persons who filled prescriptions for multiple different strengths of statins (4942 [19.4%]) and nonusers (9522 [37.5%]) were excluded from Model 2. Model 3 assessed whether statin type was associated with the hazard for OAG. Statin users were categorized into those who exclusively filled prescriptions for lovastatin, cerivastatin, atorvastatin, rosuvastatin, fluvastatin, pravastatin, and simvastatin; for each group, the OAG hazard was calculated relative to atorvastatin users. Users of multiple statin types (7704 [30.3%]) and nonusers (9522 [37.5%]) were excluded. In all models, baseline LDL level was grouped in quartiles. For those with multiple recorded LDL values, we used the reading closest to the index date. Checks for correlation of model covariates identified no concerns. Statistical significance was set at *P* = .05.

Results

Among the 25420 eligible enrollees, 15898 persons (62.5%) had at least 1 record of statin use. The mean (SD) patient age was 66.1 (5.8) years; 14112 patients (55.5%) were female, 19232 (84.1%) were white, 1252 (5.5%) were black, and 1558 (6.8%) were Latino. A total of 1218 persons (4.8%) developed OAG over a median follow-up of 440 days (Table 1). Among statin users, 3099 (19.5%) filled prescriptions exclusively for 10 mg daily, 2882 (18.1%) for 20 mg daily, 1857 (11.7%) for 40 mg daily, and 356 (2.2%) for 80 mg daily; the remaining 7704 (48.5%) received more than 1 strength. The most widely used statin agent was atorvastatin (5492 [34.6%]), followed by simvastatin (3271 [20.6%]), pravastatin (968 [6.1%]), lovastatin (616 [3.9%]), rosuvastatin (387 [2.4%]), fluvastatin (191 [1.2%]), and cerivastatin (31 [0.2%]). The remaining patients (4942 [31.1%]) used multiple agents. The mean (SD) LDL value among patients was 112 (33) mg/dL (to convert to millimoles per liter, multiply by 0.0259).

After adjusting for possible confounders and baseline LDL level, every additional month of statin use was associated with a 1% decreased hazard for OAG (hazard ratio [HR], 0.990; 95% CI, 0.983–0.998; P= .02). Thus, those who took statins continuously for 2 years had a 21% decreased hazard for OAG compared with nonusers. The difference between users and nonusers of other cholesterol-lowering medications was not significant for OAG risk (HR, 1.00; 95% CI, 0.99–1.01; P= .69). The OAG hazard among persons in the lowest baseline LDL quartile did not differ with persons in any other LDL quartile (P> .05 for all comparisons) (Table 2). The hazard did not differ between users of 40 mg daily and those taking 10 mg (HR, 0.82; 95% CI, 0.61–1.11; P= .20), 20 mg (HR, 0.92; 95% CI, 0.69–1.23; P= .58), or 80 mg (HR, 1.03; 95% CI, 0.59–1.80; P= .91) daily (Figure; Table 2). Compared with atorvastatin users, the risk of OAG was similar for persons taking lovastatin (HR, 1.09; 95% CI, 0.71–1.68; P= .69), cerivastatin (HR, 0.61, 95% CI, 0.09–4.41; P= .63), rosuvastatin (HR, 0.83; 95% CI, 0.48–1.44; P= .51), fluvastatin (HR, 0.89; 95% CI, 0.39–2.02; P= .78), pravastatin (HR, 1.29; 95% CI, 0.93–1.79; P= .13), or simvastatin (HR, 1.03; 95% CI, 0.83– 1.29; P= .78) (Table 2).

Discussion

This study offers use ful in formation a bout key parameters to consider in planning an RCT to test whether statins protect against OAG development or progression. The risk of developing OAG does not appear to be associated with the daily dosage consumed (10, 20, or 80 mg vs 40 mg). Because the risk of adverse effects rises with increasing daily statin dosage,[14] exposing RCT participants to a relatively high dosage of 80mg would seem unnecessary.A daily dosage of 40 mg or less may be more appropriate. Additionally, compared with atorvastatin, no other statin type was more protective against OAG. Because some statins are costlier than others, it seems reasonable to select an inexpensive generic agent like atorvastatin for an RCT. Finally, we found that the apparent protective effect of statins against OAG observed in our earlier study appears to persist in the present analyses after adjusting for baseline LDL levels.There was no significant difference in OAG risk between those in the highe stand lowest baseline LDL quartile safter we accounted foruse of statin and other cholesterollowering medications. This suggests that the potential beneficial

effect of statins on OAG risk is associated less with lowering lipid levels and more with other properties of statins, such as outflow enhancement by affecting rho kinase activity or neuroprotection.[13–15]Infact,the risk reduction of 2years' continuous statin use was 8% before baseline LDL level adjustment and 21% afterward

Limitations

This study had limitations.Unfortunately,claims data lackin formation on clinical variables,such a sintraocular pressures, to consider in our models. Also, we assume that filling medication prescriptions is a reasonable surrogate for medication consumption.However,if persons are filling prescriptions but not actually taking the medications, then this would bias the results to the null.

Conclusions

These study findings provide researchers with useful information about an appropriate daily dosage and type of statin to select for an RCT to explore whether statins can prevent the development of OAG or halt OAG progression.

Acknowledgments

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Key Points

Question

Does the protective effect of statins affect the risk of glaucoma depending on the daily dosage or type of statin taken?

Findings

This study found that after accounting for baseline low-density lipoprotein levels, persons who filled prescriptions for statins continuously for 2 years had a 21% reduced risk of glaucoma vs nonusers. There was no additional protective effect associated with taking the highest dosage of statins (80 mg) compared with a lower dosage (40 mg) or with other types compared with atorvastatin.

Meaning

When planning clinical trials to study the effect of statins on glaucoma, it is reasonable to use a generic statin like atorvastatin and a 40mg or lower daily dosage.
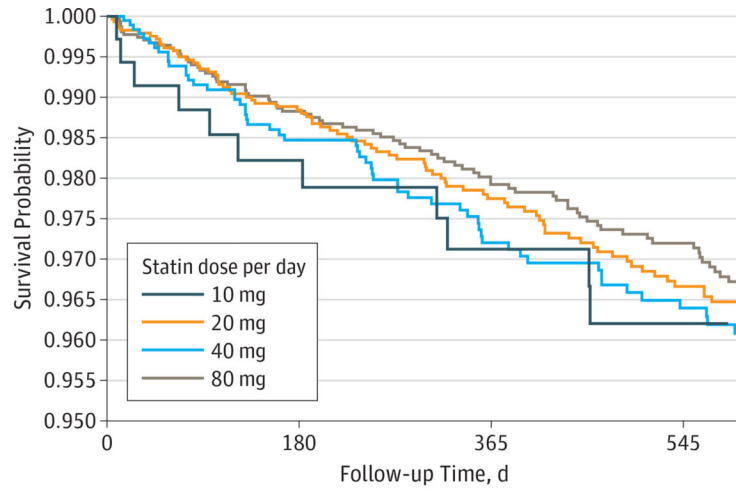
Figure. Probability of Developing Open-Angle Glaucoma Among Users of Different Daily Dosages of Statins

Survival probability is the unadjusted probability of not developing open-angle glaucoma by that time. Although not shown, the confidence bands for the 4 daily dosages overlap for nearly the entire length of follow-up, indicating no statistically significant differences.

Table 1.

Characteristics of the Study Participants

Characteristic	No. (%)			P Value
	Overall	No OAG	OAG	
Total	25420 (100)	24202 (95.2)	1218 (4.8)	
Age, mean (SD), y	66.1 (5.8)	66.1 (5.8)	66.6 (5.9)	.003
Race/ethnicity[a]				
White	19 232 (84.1)	18 398 (84.6)	834 (75.5)	
Black	1252 (5.5)	1127 (5.2)	125(11.3)	<.001
Latino	1558 (6.8)	1458 (6.7)	100 (9.1)	
Asian	600 (2.6)	565 (2.6)	35 (3.2)	
Other	218 (1.0)	208 (1.0)	10 (0.9)	
Sex				
Male	11308 (44.5)	10767 (44.5)	541 (44.4)	.96
Female	14112 (55.5)	13435 (55.5)	677 (55.6)	
Any statin used[b]	15 898 (62.5)	15152 (62.6)	746 (61.3)	.34
Type of statin used exclusively[b]				
Lovastatin	616 (3.9)	586 (3.9)	30 (4.0)	
Cerivastatin	31 (0.2)	29 (0.2)	2 (0.3)	
Atorvastatin	5492 (34.6)	5253 (34.7)	239 (32.0)	
Rosuvastatin	387 (2.4)	371 (2.5)	16(2.1)	.59
Fluvastatin	191 (1.2)	182 (1.2)	9(1.2)	
Pravastatin	968 (6.1)	921 (6.1)	47 (6.3)	
Simvastatin	3271 (20.6)	3126 (20.6)	145 (19.4)	
Using multiple statin types	4942 (31.1)	4684 (30.9)	258 (34.6)	
Other cholesterol-lowering medication use	6356 (25.0)	6062 (25.1)	294 (24.1)	.47
Statin strength used exclusively, mg[b]				
10	3099 (19.5)	2972 (19.6)	127 (17.0)	
20	2882 (18.1)	2751 (18.2)	131 (17.6)	.38
40	1857 (11.7)	1768 (11.7)	89(11.9)	
80	356 (2.2)	336 (2.2)	20 (2.7)	
Using multiple statin strengths	7704 (48.5)	7325 (48.3)	379 (50.8)	
Baseline LDL cholesterol level, mg/dL				
<82	4541 (17.9)	4326 (17.9)	215(17.7)	
82–130	13 623 (53.6)	12 988 (53.7)	635 (52.1)	.62
130–177	6339 (24.9)	6017 (24.9)	322 (26.4)	
177–225	917 (3.6)	871 (3.6)	46 (3.8)	

Abbreviations: LDL, low-density lipoprotein; OAG, open-angle glaucoma.

[a] Excluding 2560 with missing data on race/ethnicity.

[b] Excluding 9522 who were not taking statins.

Table 2.

Factors Affecting the Hazard of Developing Open-Angle Glaucoma[a]

Variable	Adjusted HR (95% CI)	*P* Value
Model 1[b]		
TD statin use	0.99 (0.98–1.00)	.02
TD use of other cholesterol-lowering medications	1.00 (0.99–1.01)	.69
LDL cholesterol level, mg/dL		
<82	1 [Reference]	NA
82–130	0.88 (0.74–1.04)	.13
130–177	0.93 (0.76–1.13)	.43
177–225	0.94 (0.66–1.34)	.74
Model 2		
40 mg of statins daily	1 [Reference]	NA
10 mg of statins daily	0.82 (0.61–1.11)	.20
20 mg of statins daily	0.92 (0.69–1.23)	.58
80 mg of statins daily	1.03 (0.59–1.80)	.91
Model 3		
Atorvastatin	1 [Reference]	NA
Lovastatin	1.09 (0.71–1.68)	.69
Cerivastatin	0.61 (0.09–4.41)	.63
Rosuvastatin	0.83 (0.48–1.44)	.51
Fluvastatin	0.89 (0.39–2.02)	.78
Pravastatin	1.29 (0.93–1.79)	.13
Simvastatin	1.03 (0.83–1.29)	.78

Abbreviations: HR, hazard ratio; LDL, low-density lipoprotein; NA, not applicable; TD, time-dependent.

[a] All 3 models adjusted for age (implicitly), sex, race/ethnicity, household net worth, education level, region of residence, systemic hypotension, obesity, sleep apnea, migraine, diabetes, hypertension, cataract, pseudophakia/ aphakia, macular degeneration, diabetic retinopathy, and Charlson Comorbidity Index score.

[b] The risk reduction of the use of statins and other cholesterol-lowering medications in the model is for each additional month of continuous use of these medications.