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Association Between Statin Use and Open-angle Glaucoma in Hyperlipidemia Patients

A Taiwanese Population-based Case-control Study

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Abstract: The aim of the study was to investigate the association between statin use and open-angle glaucoma (OAG) risk in hyperlipidemia patients.

We used the research database of the Taiwan National Health Insurance program to conduct a population-based case-control study. A total of 1276 patients with newly diagnosed OAG were identified from 2004 to 2011. Controls comprised of 12,760 patients without glaucoma and were frequency-matched for age, sex, history of diabetes mellitus, and year of hyperlipidemia diagnosis at a 1:10 ratio. Accumulated defined daily doses (DDDs) of statins prescribed during follow-up were calculated. Average statin use was calculated as the sum of DDDs divided by the duration from the initial statin prescription date to the index date (per year), and was subdivided into 3 levels: <30, 30 to 119, and ≥120 DDDs. Comorbidity, including hypertension, depression, and the Charlson comorbidity index, the frequency of eye care visits, and the use of nonstatin cholesterol-lowering drugs, were all considered as confounding factors.

For the group with statin use, the adjusted odds ratio of OAG was 1.02 (95% confidence interval 0.90–1.15) when compared with the group without statin use. Subanalysis showed that a high dosage of statin use (≥120 DDD/y) resulted in a1.24-fold increased risk of OAG (odds ratio 1.24, 95% confidence interval 1.03–1.49). The incidence of OAG was increased with the increase of the dosage of statin use (*P* for trend = 0.0458).

Clinicians should be cautious of hyperlipidemia patients with a high dosage of statin use because it might be associated with an increased risk of OAG. Ophthalmologist consultation is necessary for this high-risk group.

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Abbreviations: CIs = confidence intervals, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, NHIRD = National Health Insurance Research Database, OAG = Open-angle glaucoma, OR = odds ratio, SD = standard deviation.

INTRODUCTION

Primary open-angle glaucoma (OAG) is a disease characterized by the irreversible loss of retinal ganglion cells, ultimately resulting in the loss of sight,[1] and it is a prevalent type of glaucoma in the Taiwanese population.[2,3] Statins act as selective inhibitors of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase and are widely used medications to lower cholesterol in patients with hyperlipidemia.[4] Reports on whether statins are beneficial in patients with OAG have been inconsistent.[4] Some studies have suggested that statins may be protective againstOAG,[4–8] whereas others have reported contradictory results.[9,10] The possible protective effect of stain might be due to the increased aqueous outflow caused by inhibiting rho-kinase activity.[11] In addition, statins have been shown to prevent neuronal cell death in retina ischemic injury models.[7,12]

The purpose of this study is to determine the association between statin use and incident OAG in our population. We used a large nationwide healthcare claims database containing detailed medical records of all Taiwanese residents with hyperlipidemia. To our knowledge, no study has been published investigating this crucial issue in a Taiwanese population.

METHODS

Data Source

The Taiwan National Health Insurance program (Taiwan NHI) was established in 1995, and it is a nationwide single-

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H-YC, S-YH, and C-HK conceived and designed the experiments; all authors performed the experiments and analyzed the data; C-HK contributed reagents/materials/analysis tools; and all authors wrote and approved the manuscript.
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payer health insurance program. The Taiwan NHI is compulsory for all citizens and its coverage has included more than 99% of Taiwan's 23 million residents since 1998. The Taiwan government entrusted National Health Research Institutes (NHRI) to establish and manage the National Health Insurance Research Database (NHIRD), which contains all historical reimbursement claims data from Taiwan NHI.[13] Before NHRI emancipated the database for research, all personal identification information was encrypted to ensure patient privacy. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

The study population was derived from the Longitudinal Health Insurance Database (LHID), which is a subset of the NHIRD. NHRI randomly sampled one million beneficiaries from 1996 to 2000 from the NHIRD. On the basis of the report from NHRI, there are no differences in age and sex distributions between the LHID and NHIRD. The LHID contains annual claims records including the beneficiary registry, outpatient and inpatient visits, the drug prescription registry, and other medical service. NHRI provided an anonymous identification number to link each patient's claims data because of the encrypted identification information.

In this study, the disease history of each study population was collected from the outpatient (including emergent department visits) and inpatient data. The disease record in the NHIRD was based on the criteria of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study Population

This study was designed as a population-based case-control study. The case group comprised of newly diagnosed OAG patients (ICD-9-CM 365.1, 365.10, 365.11, 365.12, and 365.15) with hyperlipidemia history (ICD-9-CM 272), from 2004 to 2011. We provided an index date as the initial OAG diagnosis date for the case group. The control group was randomly selected from patients without glaucoma diagnosis (ICD-9-CM 365) and was frequency-matched by age (per 5 y), sex, history of diabetes mellitus (ICD-9-CM 250), and year of hyperlipidemia diagnosis at a 1:10 ratio. The index date for the control group was randomly assigned a day and month with the same index year as the matched case.

The major interesting factor was statin use (ATC code: C10AA). We collected all statin prescriptions for each study patient before the index date. The statins included the following subtypes: simvastatin (ATC code: C10AA01), lovastatin (ATC code: C10AA02), pravastatin (ATC code: C10AA03), fluvastatin (ATC code: C10AA04), atorvastatin (ATC code: C10AA05), and rosuvastatin(ATC code: C10AA07). To standardize the statin use for each study patient, accumulated defined daily doses (DDDs) prescribed during follow-up were calculated. The average statin use was calculated as the sum of DDDs divided by the duration from the initial statin prescription date to the index date (per year), and was subdivided into 3 levels: <30, 30 to 119, and ≥ 120 DDDs.

Comorbidity was considered as a confounding factor in this study. Comorbidity was defined as the disease history before the index date and included hypertension (ICD-9-CM 401-405), depression (ICD-9-CM 296.2, 296.3, 300.4, 301.12, 309.0, 309.1, and 311), and the Charlson comorbidity index (CCI). The CCI is a weighted score of major diseases.[14,15] We categorized 4 levels of the CCI as 0, 1 to 2, 3 to 5, and 6 or higher. We also considered the effect of nonstatin cholesterol-lowering drug use, defined as patients with cholesterol-lowering drug treatment, from the date of hyperlipidemia diagnosis to the index date. Other nonstatin cholesterol-lowering drugs included acipimox (ATC code: C10AD06), gemfibrozil (ATC code: C10AB04), fenofibrate (ATC code: C10AB05), inositol niacinate (ATC code: C04AC03),and xanthinolniacinate (ATC code: C04AD02). The year of hyperlipidemia diagnosis was adjusted in the analysis. Eye care visits were also considered as a confounding factor, and was calculated using the frequency of eye care visits from the hyperlipidemia diagnosis date to the index date.

Statistical Analysis

To describe the structure of the study population, the age distribution was expressed as a mean and standard deviation (SD), and the distribution of sex, statin exposure, and comorbidities were expressed as numbers and proportions. The t test for age and chi-square test for category variables were used to assess the distribution difference between the OAG and control groups. To evaluate the association between statin use and OAG risk, simple and/or multiple logistic regressions were performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). All data management and analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC). All tests used were 2-sided. Statistical significance was defined as $P < 0.05$.

RESULTS

Table 1 shows the distribution of demographic factors, comorbidities, and statin use between the OAG group and control group. The 2 groups had a similar mean age (64 y) and the same sex ratio (50.5% male). Depression was the only comorbidity with a higher percentage in the OAG group than in the control group. The mean frequency of eye care visits in the OAG group was significantly higher than that in the control group (27.8 vs 12.4; $P < 0.0001$). Nearly 55% of the OAG patients ever with statins use and only 53% of the control patients used statins. The percentage of nonstatin cholesterol-lowering drug use exhibited no difference between the OAG group and control group (all $P > 0.05$).

Table 2 shows the effect of statin use and the risk of OAG. After adjustment for age, sex, hypertension, depression, the CCI level, the frequency of eye care visits, year of hyperlipidemia diagnosis, and the use of nonstatin cholesterol-lowering drugs, patients with statin use were not significantly associated with OAG (OR 1.02, 95% CI 0.90–1.15) compared with patients without statin use. In further subanalysis, we observed that patients with a high dosage of statin exposure (≥ 120 DDD/y) had a 1.24-fold increased risk of OAG (OR 1.24, 95% CI 1.03–1.49). The results also revealed that the incidence of OAG was increased with the increase of the dosage of statin exposure ($P = 0.0458$).

Table 3 presents the association between different subtypes of statin use and OAG. After adjustment for age, sex, hypertension, depression, the CCI level, the frequency of eye care visits, year of hyperlipidemia diagnosis, and the use of nonstatin cholesterol-lowering drugs, the results revealed that there was no statistical significance between any subtype of statin use and the risk of OAG.

DISCUSSION AND CONCLUSIONS

Several studies have attempted to elucidate the relationship between statin use and glaucoma. However, contradictory

TABLE 1. Demographic Status and Comorbidity Compared Between Control Group and OAG Group

Variables	Control Group (n = 12729 [%])	OAG Group (n = 1276 [%])	*P* Value
Age, y (SD)*	64.1 (12.4)	64.1 (12.6)	0.8475
Sex			
Female	6302 (49.5)	632 (49.5)	0.9887
Male	6427 (50.5)	644 (50.5)	
Statin exposure			
No	5917 (46.5)	572 (44.8)	0.2578
Yes	6812 (53.5)	704 (55.2)	
Statin average exposure (DDD/y)			0.0080
None	5917 (46.5)	572 (44.8)	
<30	2516 (19.8)	221 (17.3)	
30–119	2709 (21.3)	290 (22.7)	
≥120	1587 (12.5)	193 (15.1)	
Comorbidity			
Hypertension	9521 (74.8)	980 (76.8)	0.1150
DM	5849 (46.0)	588 (46.1)	0.9285
Depression	1485 (11.7)	180 (14.1)	0.0102
CCI, mean (SD)	0.6 (1.3)	0.6 (1.2)	0.87
0	8983 (70.6)	892 (69.9)	
<3	2649 (20.8)	275 (21.6)	
3–5	941 (7.4)	98 (7.7)	
≥6	156 (1.2)	11 (0.9)	
Number of visits to eye care, mean (SD)	12.4 (22.5)	27.8 (36.3)	<0.0001
0	3256 (25.6)	70 (5.5)	
<5	3675 (28.9)	220 (17.2)	
5–16	2981 (23.4)	388 (30.4)	
>16	2817 (22.1)	598 (46.9)	
Other nonstatin cholesterol-lowering drugs			
Acipimox	208 (1.6)	18 (1.4)	0.5460
Gemfibrozil	3252 (25.5)	304 (23.8)	0.1775
Fenofibrate	1982 (15.6)	193 (15.1)	0.6754
Inositol niacinate	148 (1.2)	12 (0.9)	0.4763
Xanthinol niacinate	97 (0.8)	12 (0.9)	0.4893

CCI = Charlson comorbidity index, DDD = defined daily dose, OAG = open-angle glaucoma, SD = standard deviation.
* *t* test.

results have been noted across studies.[4–10] In the study by Stein et al,[4] statin use was found to be associated with a significant reduction in the risk of OAG among hyperlipidemia patients aged above 60 years by using a claims database from the USA. McGwin et al[5] reported that statin use longer than 24 months was associated with a lower risk of OAG in male patients aged 50 years and older. In the prospective study by Leung et al,[6] simvastatin use was reported to be possibly associated with visual field stabilization in patients with normal-tension glaucoma. In another study proposed by De Castro et al,[7] statin drugs were found to be associated with a slowed progression of optic nerve parameters in a glaucoma suspect, measured using confocal scanning laser ophthalmoscopy. In the prospective population-based cohort study by Marcus et al,[8] long-term use of statins seemed to be associated with a reduced risk of OAG. In contrast to the 5 aforementioned studies, 2 other studies showed no relationship between statin use and glaucoma.[9,10] Owen et al[9] found that statins do not have a preventive role in glaucoma on the basis of a primary care database in the United Kingdom. In a similar claims database study from Canada,[10] the authors reported that statin use made no significant difference in the need for adjunct glaucomatherapy. In our study, we first report that glaucoma risk in the group with statin use was the same as that in the group without statin use in hyperlipidemia patients in the Taiwanese population (adjusted OR 1.01, 95% CI 0.89–1.14), and that a high dosage of statin use (≥120 DDD/y) resulted in a 1.26-fold increased risk of OAG (OR 1.26, 95% CI 1.05–1.51) compared with no stain use. Our findings conflict with the prevailing literature. However, our study cannot be directly compared with others because of the different study design and methodology used. We argue that one plausible reason for our findings is the prescription policy in the Taiwan NHI system.[15] To control the cost of medicine, the Taiwan NHI bureau has strict guidelines for statin prescription. They approve statin use only in patients with severe hyperlipidemia; the detailed criteria are as follows: total cholesterol (TC) level ≥160 mg/dL or low-density lipoprotein-C (LDL-C) level ≥100 mg/dL, with comorbidity of coronary artery disease, ischemic cerebrovascular disease, or diabetes mellitus; TC level ≥200 mg/dL or LDL-C level ≥130 mg/dL, with ≥2 risks (including hypertension, males aged ≥45 y, females aged ≥55 y); family history of coronary artery disease, high-density lipoprotein-C (HDL-C) <40 mg/dL, or smoking; total triglyceride (TG) level ≥200 mg/dL, with TC/HDL-C >5 or HDL-C

TABLE 2. Logistic Regression Analysis Measured Odds Ratio for the OAG Between the Individual With and Without Statin Exposure

Variables	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
Statin exposure		
No	ref	ref
Yes	1.07 (0.95–1.20)	1.02 (0.90–1.15)
Average statin exposure (DDD/y)		
None	ref	ref
<30	0.91 (0.77–1.07)	0.87 (0.73–1.03)
30–119	1.11 (0.95–1.28)	1.03 (0.88–1.21)
≥120	1.26 (1.06–1.49)	1.24 (1.03–1.49)
P value for trend	0.0085	0.0458
Age group		
<50	ref	
50–64	0.99 (0.82–1.19)	
≥65	0.99 (0.83–1.18)	
Sex		
Female	ref	
Male	1.00 (0.89–1.12)	
Hypertension	1.12 (0.97–1.28)	
Depression	1.24 (1.05–1.47)	
CCI level		
0	ref	
<3	1.05 (0.91–1.20)	
3–5	1.05 (0.84–1.31)	
≥6	0.71 (0.38–1.31)	
Number of visits to eye care		
0	ref	
<5	2.78 (2.12–3.66)	
5–16	6.05 (4.67–7.85)	
>16	9.87 (7.67–12.71)	
Year of hyperlipidemia diagnosis		
<5	ref	
5–9	0.98 (0.85–1.12)	
≥10	0.98 (0.84–1.14)	
Nonstatin cholesterol-lowering drugs		
Acipimox	0.86 (0.53–1.40)	
Gemfibrozil	0.91 (0.80–1.04)	
Fenofibrate	0.97 (0.82–1.13)	
Inositol niacinate	0.81 (0.45–1.46)	
Xanthinol niacinate	1.24 (0.68–2.26)	

CCI = Charlson comorbidity index, CI = confidence interval, DDD = defined daily dose, OAG = open-angle glaucoma.

* Model adjusted for age, sex, hypertension, depression, CCI level, number of visits to eye care, year of hyperlipidemia diagnosis, Acipimox, Gemfibrozil, Fenofibrate, Inositol niacinate, and Xanthinol niacinate.

TABLE 3. Logistic Regression Analysis Measured Odds Ratio for Different Subtypes of Statin Exposure and the Risk of OAG

Variables	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
Simvastatin	1.12 (0.97–1.29)	1.09 (0.93–1.27)
Lovastatin	0.95 (0.83–1.10)	0.86 (0.74–1.01)
Pravastatin	1.22 (1.02–1.45)	1.19 (0.98–1.44)
Fluvastatin	1.25 (1.05–1.48)	1.18 (0.98–1.42)
Atorvastatin	1.03 (0.90–1.17)	0.90 (0.78–1.05)
Rosuvastatin	0.97 (0.79–1.20)	0.93 (0.74–1.17)

CI = confidence interval, OAG = open-angle glaucoma.

* Model adjusted for age, sex, hypertension, depression, CCI level, number of visits to eye care, year of hyperlipidemia diagnosis, Acipimox, Gemfibrozil, Fenofibrate, Inositol niacinate, and Xanthinol niacinate.

<40 mg/dL, with comorbidity of coronary artery disease, ischemic cerebrovascular disease, or diabetes mellitus; TG ≥500 mg/dL. Furthermore, blood cholesterol level should be followed after 3 months of statin treatment. If the CL/TG concentration improves and does not satisfy the aforementioned criteria, the clinician is not allowed to prescribe statin. On the basis of this policy, cases with a higher dosage of statin prescription usually means a poorer lipid control condition. The risk of glaucoma is likely to be relatively higher in cases with a higher dosage of statin prescription compared with those with a lower dosage. On the basis of the literature, statins have been shown to increase aqueous outflow facility.[16,17] However, in the current result, there was no statistical significance between any subtype of statin use and the risk of OAG. Further observation is crucial in this issue.

In recent epidemiologic studies from Taiwan, OAG has been found to be significantly associated with comorbidities.[18,19] Therefore, we considered the CCI to be a favorable variable to adjust for the overall health of the patients in this study. Furthermore, the frequency of eye care visits might bias glaucoma diagnosis; hence, we also considered this as a confounding factor. Although the glaucoma group had more eye care visits and depression incidences than did the control group, after adjustment of all of these confounding factors, statin use was still not associated with a higher OAG risk. Therefore, we believe that the current findings are valid.

However, our study also has some limitations. First, we defined glaucoma on the basis of claims data (ICD-9 coding from clinicians), which may be less accurate than diagnoses performed individually through a standardized procedure. In a claims database study, clinical information such as intraocular pressure, central corneal thickness, visual field findings, and optic nerve evaluation are not available. Therefore, we were unable to determine with certainty whether all newly diagnosed OAG patients had the condition, nor could we fully obtain the disease severity. Second, selection bias existed in this study. Because the NHIRD only included patients who sought treatment, those who did not seek help may have been recruited into the control group. Third, despite the large sample size, the study cohort consisted of only the Taiwanese population, and thus the findings cannot be easily generalized to other population groups. Fourth, the Taiwan NHI bureau has strict guidelines for statin prescription, which means that statin users should be patients with severe hyperlipidemia. This may affect patients' access to healthcare service, including eye care service, thus increasing the likeliness of patients receiving an OAG diagnosis. Lastly, blood cholesterol levels of the patients before and after statin use were not available for comparison. The accumulated DDDs prescribed during follow-up were calculated, but we did not know about the compliance of patients and their

adherence to therapy prescription. Despite the aforementioned limitations, our study has some notable strengths. First, the database is large and has favorable sample randomization, and we could follow patients over time to assess the relationship between statin exposure and subsequent OAG. Second, this dataset includes data on a diverse range of patients with different sociodemographic profiles, unlike some smaller studies that have recruited patients from a specific region, which might not represent the whole population. Third, the current study is one of the few studies evaluating the relationship between statin prescription and OAG risk in a Taiwanese hyperlipidemia population based on a large claims database. Because we are not yet clear about the exact mechanism why a higher dosage of statin use might lead to a higher glaucoma risk, further detailed study should be conducted to clarify this issue.

In sum, clinicians should be cautious of hyperlipidemia patients with a high dosage of statin use because it might be associated with an increased risk of OAG. Ophthalmologist consultation is necessary for this high-risk group.

REFERENCES

1. Marcus MW, Müskens RP, Ramdas WD, et al. Antithrombotic medication and incident open-angle glaucoma. *Invest Ophthalmol Vis Sci.* 2012;53:3801–3805.
2. Chen HY, Chang YC, Wang IJ, et al. Comparison of glaucoma diagnoses using Stratus and Cirrus optical coherence tomography in different glaucoma types in a Chinese population. *J Glaucoma.* 2013;22:638–646.
3. Chen HY, Chang YC, Chen WC, et al. Association between plasma endothelin-1 and severity of different types of glaucoma. *J Glaucoma.* 2013;22:117–122.
4. Stein JD, Newman-Casey PA, Talwar N, et al. The relationship between statin use and open-angle glaucoma. *Ophthalmology.* 2012;119:2074–2081.
5. McGwin G Jr, McNeal S, Owsley C, et al. Statins and other cholesterol-lowering medications and the presence of glaucoma. *Arch Ophthalmol.* 2004;122:822–826.
6. Leung DY, Li FC, Kwong YY, et al. Simvastatin and disease stabilization in normal tension glaucoma: a cohort study. *Ophthalmology.* 2010;117:471–476.
7. De Castro DK, Punjabi OS, Bostrom AG, et al. Effect of statin drugs and aspirin on progression in open-angle glaucoma suspects using confocal scanning laser ophthalmoscopy. *Clin Exp Ophthalmol.* 2007;35:506–513.
8. Marcus MW, Müskens RP, Ramdas WD, et al. Cholesterol-lowering drugs and incident open-angle glaucoma: a population-based cohort study. *PLoS One.* 2012;7:e29724.
9. Owen CG, Carey IM, Shah S, et al. Hypotensive medication, statins, and the risk of glaucoma. *Invest Ophthalmol Vis Sci.* 2010;51:3524–3530.
10. Iskedjian M, Walker JH, Desjardins O, et al. Effect of selected antihypertensives, antidiabetics, statins and diuretics on adjunctive medical treatment of glaucoma: a population based study. *Curr Med Res Opin.* 2009;25:1879–1888.
11. Rao PV, Deng PF, Kumar J, et al. Modulation of aqueous humor outflow facility by the Rho kinase-specific inhibitor Y-27632. *Invest Ophthalmol Vis Sci.* 2001;42:1029–1037.
12. Honjo M, Tanihara H, Nishijima K, et al. Statin inhibits leukocyte-endothelial interaction and prevents neuronal death induced by ischemia-reperfusion injury in the rat retina. *Arch Ophthalmol.* 2002;120:1707–1713.
13. National Health Insurance Research Database. http://w3.nhri.org.tw/nhird//en/index.htm. Taiwan, 2011.
14. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* ;40:373–383.
15. Deyo RA, Cherkin DC, Ciol MS. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45:613–619.
16. Song J, Deng PF, Stinnett SS, et al. Effects of cholesterol-lowering statins on the aqueous humor outflow pathway. *Invest Ophthalmol Vis Sci.* 2005;46:2424–2432.
17. Villarreal G Jr, Chatterjee A, Oh SS, et al. Rhee DJ. Pharmacological regulation of SPARC by lovastatin in human trabecular meshwork cells. *Invest Ophthalmol Vis Sci.* 2014;55:1657–1665.
18. Lin HC, Chien CW, Hu CC, et al. Comparison of comorbid conditions between open-angle glaucoma patients and a control cohort: a case-control study. *Ophthalmology.* 2010;117:2088–2095.
19. Chen HY, Chang YC, Lin CC, Chen WC. Obstructive sleep apnea patients having surgery are less associated with glaucoma. *J Ophthalmol.* 2014;2014:838912. doi: 10.1155/2014/838912. Epub 2014 Jul 24.