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Original Article

Oral Statins and Glaucomatous Visual Field Progression

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SUMMARY

Background: To evaluate the effect of oral statins on the rate of Humphrey visual field progression in patients with open angle glaucoma (OAG).
Methods: Patients with primary open angle glaucoma and normal tension glaucoma who had been regularly followed-up in our glaucoma clinic were reviewed for demographic records, statin use history, comorbid medical conditions, and visual field tests. The rate of visual field progression was compared between statin users and nonusers using pointwise liner regression. To further analyze visual field change, we divided Humphrey visual field into twelve subfields and compared the rate of progression accordingly.
Results: Sixty-one OAG statin-users and 65 age matched nonusers were enrolled in the study. The mean follow-up period was 9.0 years. The average rate of global visual field progression between the two groups was similar (-0.28 dB/year in statin group and -0.29 dB/year in non-statin group, $p = 0.856$). However, in subfield analysis, statin users had slower rate of progression in the superior-nasal area (zone 3) than in nonusers (-0.07 dB/year vs. -0.28 dB/year, $p = 0.019$).
Conclusion: The global rate of visual field progression was similar in statin users and nonusers. However, subfield analysis showed that the superior-nasal visual field declined slower in glaucoma patients who received oral statins.

1. Introduction

Glaucoma is an optic neuropathy characterized by progressive loss of neuroretinal tissue, remodeling of optic nerve head and development of visual field loss. The prevalence of glaucoma increases with advancing age.[1] For primary open-angle glaucoma (POAG), the prevalence increased from 0.6% for age 40–49, to 7.3% for people over 80 years old.[2] The visual field defect in glaucoma significantly affects patient's functional status and quality of life.[3,4] Preventing vision loss in this potentially blinding disease is a topic of increasing concern.

Statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) are cholesterol-lowering medication commonly prescribed in patients with dyslipidemia to prevent cerebrovascular and cardiovascular disease.[5,6] The mechanisms of statins to reduce the risk of cerebrovascular and cardiovascular disease are miscellaneous and may include those independent of their cholesterol-lowering properties.[7,8] The pleiotropic effects of statins had been proposed to lower intraocular pressure (IOP) and protect retinal ganglion cells against glaucomatous damage.[9,10] There had been increasing interest in the protective effect of statins in glaucoma.

At present, although many studies have found that the consumption of statin may affect the development of glaucoma,[11–15] only two studies evaluated the relationship between statin consumption and visual field (VF) progression, both using global VF indices as the measurement parameter.[16,17] However, early glaucoma usually manifests as a localized visual field change, which may be ignored on global indices. Pointwise linear regression (PLR) is another way to evaluate VF progression. It reveals the regression of retinal threshold sensitivity over time at each test location and provides an estimate for the rate of change at each test location in the visual field. PLR analysis has been used frequently in research settings to detect visual field progression.[18–22] The current study evaluated the effect of oral statin consumption on VF progression using PLR.

2. Methods

This study was approved by the Chang Gung Medical Foundation Institutional Review Board (202100686B0) and was conducted in accordance with the tenets set forth in the Declaration of Helsinki.

Retrospectively we enrolled patients diagnosed as having primary open angle glaucoma (POAG) and normal tension glaucoma (NTG) at the Department of Ophthalmology of Chang Gung Memorial Hospital, Linkou, Taiwan from 2002/11/01 to 2018/10/30. The glaucoma patients who had received at least five reliable visual field tests were included for further evaluation. All visual field tests were performed regularly every 6 months using the Humphrey Field Analyzer (Carl Zeiss Meditec Inc, Dublin, California, USA) with a 30-2

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test pattern, size III white stimulus Swedish interactive threshold algorithm (SITA) standard program. The reliability criteria were set as: false-positive rates < 15%, false-negative rates < 30%, and fixation losses < 20%. The exclusion criteria were prior ocular surgery or laser iridotomy, glaucoma suspect, primary angle closure glaucoma or secondary glaucoma. Results of serum lipid profile and blood pressure were also documented.

The enrolled glaucoma patients were subsequently divided into two groups according to whether oral statins were used during this follow-up period. Patients in the statin group had oral statins throughout the time of follow-ups. The rate of VF progression between the two groups were compared. When evaluating VF progression, the 74 test locations of the 30-2 Humphrey visual field were divided into 10 zones according to the glaucoma hemifield test (GHT) sectors, and the remaining temporal-peripheral area were further divided into 2 zones, making a total 12 zones (Figure 1). Zone 1 to 6 were in the upper hemifield and zone 7 to 12 were in the lower hemifield. The VF sensitivity in each zone was averaged and the rate of visual field progression (dB/year) were calculated. Data were expressed as mean ± standard deviation (SD) for continuous variables and percentage for categorical variables. The computational statistical environment R (http://www.r-project.org) was used to carry out large-scale pointwise linear regression analyses. Categorical variables were compared using the X^2 test, whereas continuous variables were compared using an independent t test. $p < 0.05$ indicated statistical significance.

3. Results

In total, 126 patients with POAG or NTG were enrolled. There were 61 patients in the statin group and 65 in the non-statin group. The demographic data between the two groups was shown in Table 1. There were no significant difference in age, gender distribution, visual acuity, intraocular pressure, number of glaucoma medication, baseline visual field mean deviation, and follow-up period between the two groups. Physical and laboratory examination showed no significant difference in blood pressure, body height, creatinine, serum glucose, high-density lipoprotein (HDL) and uric acid level between the two groups. However, the statin group had more comorbidity. Compared with non-statin group, the total cholesterol and low-density lipoprotein (LDL) level were lower (p = 0.004 and 0.028, respectively), and the mean body weight was higher (p = 0.031) in the statin group. Atorvastatin and rosuvastatin were the most frequently prescribed statins. The types of statins used was shown in Table 2.

Table 1
Clinical characteristics of patients.

	Statin group	Non-statin group	p value
Patient number	61	65	
Age at recruitment	51.2	50.0	0.469
Sex (male/female)	4.55	2.10	0.066
Systemic disease			
Hypertension	32 (52.4%)	9 (13.8%)	< 0.001*
Diabetes mellitus	20 (32.8%)	0 (0%)	< 0.001*
Dyslipidemia	50 (90.0%)	5 (7.7%)	< 0.001*
Renal disease	6 (9.8%)	2 (3.1%)	0.155
CVA	6 (9.8%)	0 (0%)	0.011*
CAD	11 (18.0%)	2 (3.1%)	0.007*
Physical and laboratory exam.			
Systolic blood pressure (mmHg)	129.5	127.2	0.517
Diastolic blood pressure (mmHg)	76.4	78.0	0.514
Body height (cm)	165.2	166.2	0.600
Body weight (kg)	69.0	62.6	0.027*
Creatinine (mg/dL)	1.11	0.83	0.268
ALT (U/L)	24.8	27.3	0.435
Glucose (mg/dL)	108.2	99.5	0.111
Cholesterol (mg/dL)	176.5	202.0	0.005*
HDL (mg/dL)	50.5	52.3	0.589
LDL (mg/dL)	100.4	124.0	0.007*
TG	1.12	0.83	0.268
Uric acid (mg/dL)	5.91	5.71	0.564
Eye number	107	106	
POAG/NTG	45/62	40/66	0.520
VA (logMAR)	0.105	0.160	0.213
Initial IOP	14.64	14.13	0.115
Initial MD	-2.47	-1.71	0.081
No. of glaucoma medication	1.74	1.80	0.664
Mean follow-up period (years)	9.0	10.6	0.790

* $p < 0.05$.
ALT = alanine aminotransferase, CAD = coronary artery disease, CVA = cerebrovascular accident, HDL = high-density lipoprotein, IOP = intraocular pressure, LDL = low-density lipoprotein, logMAR = logarithm of the minimum angle of resolution, MD = mean deviation, No. = number, NTG = normal tension glaucoma,POAG= primary open-angle glaucoma, TG = triglyceride, VA = visual acuity.

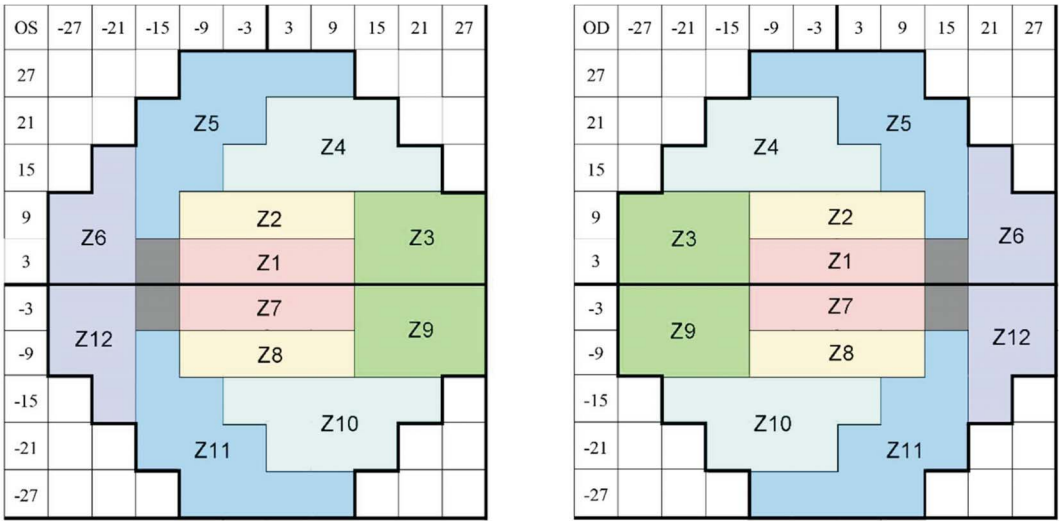

Figure 1. The twelve zones of visual subfield analysis. The 74 test locations of the 30-2 Humphrey visual field were divided into 10 zones according to the glaucoma hemifield test (GHT) sectors. The remaining temporal-peripheral area were further divided into 2 zones, making a total 12 zones. The two points of the blind spot was excluded.

Table 2
The types of statin used by the statin group.

Statin	N = 61	%
Atrovatstatin	28	45.9
Fluvastatin	4	6.6
Lovastatin	1	1.6
Pitavastatin	4	6.6
Rosuvastatin	21	34.4
Simvastatin	3	4.9

The average rates of global visual field progression between the two groups were not statistically significant (-0.28 dB/year in statin users and -0.29 dB/year in non-statin users, $p = 0.856$) (Table 3). Subfield analysis revealed that the rate of VF progression was similar in all zones except for zone 3, where the decline rate was significantly slower in statin users than in non-statin users (-0.07 dB/yr and -0.28 dB/yr, p = 0.019). Although statistically insignificant, statin users had faster VF decline in most of the inferior fields and slower VF decline in the superior fields (Figure 2).

Table 3
Visual field sensitivity change slope in glaucoma patients with and without statin use.

Zone	Statin (N = 107) (dB/yr)	No statin (N = 106) (dB/yr)	p value
Z1	-0.2560	-0.3025	0.650
Z2	-0.2738	-0.2986	0.748
Z3	-0.0660	-0.2811	0.019*
Z4	-0.1521	-0.2515	0.285
Z5	-0.1803	-0.2075	0.756
Z6	-0.1004	-0.1177	0.797
Z7	-0.2159	-0.2833	0.431
Z8	-0.3064	-0.2892	0.853
Z9	-0.2817	-0.2711	0.912
Z10	-0.1857	-0.2302	0.519
Z11	-0.0625	-0.2209	0.052
Z12	-0.1205	-0.0765	0.615
ZU	-0.1594	-0.2768	0.180
ZL	-0.3399	-0.2613	0.390
Zall	-0.2793	-0.2954	0.856

* $p < 0.05$.
ZU represents the upper hemifield, which is composed of Z1 to Z6. ZL represents the lower hemifield, which is composed of Z7 to Z12. Zall represents the global visual field.

4. Discussion

Previous research had suggested that statins not only prevent cardiovascular disease, but also lower the risk of POAG.[11–13,23] Talwar et al. analyzed the Clinformatics Data Mart database and found that patients who used statin had a 21% reduction in the risk of open angle glaucoma (OAG) compared to patients who did not use statin.[11] Stein et al. analyzed the national United States managed care network database and found that patients with hyperlipidemia can reduce the OAG risk by 8% after using statin for two years.[12] Marcus et al. found that the hazard ratio of OAG for statin users was 0.54 in a prospective population-based cohort study.[13] The above studies indicate that long-term use of statin reduced the incidence of OAG.

Besides, some observational studies demonstrated that oral statins decelerated VF progression in glaucoma patients. Leung et al. found that statins use was among 6.6% of patients who had VF progression and among 17% of patients without VF progression in a cohort study consisting of 256 patients over 36 months' follow-up period, indicating that statins were associated with VF stabilization.[16] In another observational study including 847 patients with a mean follow-up period of 1324 days, Whigham et al. found that 35% of patients using statins developed VF progression, whereas 56% of patients who did not use statins developed VF progression. The study indicated that statin users were less likely to develop VF progression.[17] However, the follow-up periods were only 3–4 years in both aforementioned studies. The long-term effect of oral statins on VF progression is not clear. The current study followed the patients with early OAG for near ten years and found that there was no statistically significant difference in the global rate of VF progression between statin users and non-statin users.

Some studies argued that statins provided no protective effect against glaucoma.[14,15,24] A population-based study using the Régie de l'assurance maladie du Québec database found that there was no significant difference in the use of prostaglandin analogue between patients with or without statins use.[15] Owen et al. observed over five years using UK DIN-LINK database and found no correlation between statins use and the incidence of glaucoma.[24] Chen et al. found that statin use was not associated with a significant higher risk of OAG, but the risk of developing OAG was 1.24 times higher in those who used high dosage of statin than the those without statin use.[14] The

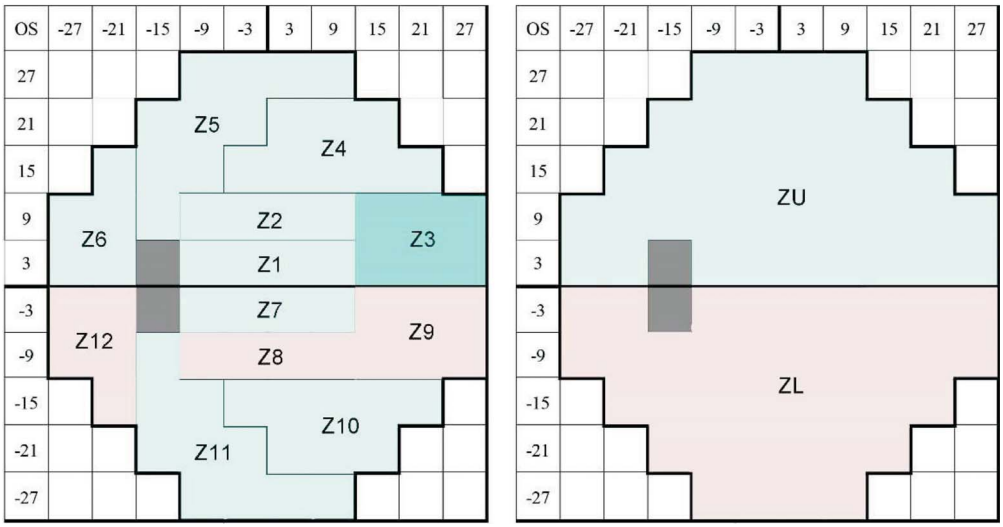

Figure 2. The effect of statins on visual field progression. The dark blue area (Z3) represents statistically significant slower visual field progression in the statin group. The light blue area shows slower progression in the statin group but did not reach a significant difference. The light red area shows faster visual field progression in the statin group, but also statistically insignificant.

Taiwan-based study using National Health Insurance Research Database concluded that the patients using high dosage of statin carried a higher risk of developing OAG, and the protective effect of statin against glaucoma was not clarified.

We proposed possible explanations why statin did not affect global VF progression. First, statins were known to be beneficial for macrovascular diseases, such as cardiovascular disease and cerebrovascular disease, its role on microvascular disease was not clear.[25] Since glaucomatous optic neuropathy is a microvascular disease, the protection of statins against glaucomatous optic neuropathy remained to be verified. Second, statins were known to raise plasma glucose level and increase the risk of developing diabetes mellitus, which may offset its protective effects.[26–28] Third, statins may cause cataract by inhibiting HMG-CoA synthase in lens, reducing sterol synthesis and isoprene-derived anti-inflammatory substances.[29,30] Several animal studies had shown that statins accelerated the development of cataract.[29,30] Other clinical studies also found that statins were associated with the development of cataract.[31,32] The development of cataract may interfere visual field testing thus blunting the protective effect of statin. In the current study, all the included glaucoma patients were phakic, thus the development of cataract associated with statin use may mask its protection effect against VF progression.

The protective effect of statin on VF progression may be different in each subfield. Unlike previous studies which focused on global rather than regional VF changes, the current study was the first one to describe the influence of oral statins on the progression of visual subfields. Our result showed that although the global VF decline rate was similar, statin users had slower progression in the nasal upper area (Zone 3) compared to non-statin users. Although the mechanism was unclear, we assumed that there were regional differences in retina blood perfusion. Zink et al. reported that the inferior temporal part of the optic disc was most vulnerable to changes in retinal blood flow, which lead to VF progression in the superior-nasal area.[33] Kim et al. confirmed that the superior-nasal VF defect was most related to systemic diseases such as essential hypertension and diabetes mellitus.[34] The pleiotropic effect of statins might increase endothelial nitric oxide synthase (eNOS), which subsequently increased nitric oxide level and caused vasodilation.[35] It was reported that statin might induce vasodilatation of retinal arterioles and venules and improved retinal blood flow.[36,37] Presumably, statins improved focal retinal and optic nerve blood flow and produced protective effects on the corresponding visual subfield.

Studies have shown that statin users often had more comorbidities, which may also affect the development of glaucoma. These comorbidities can result in interference when analyzing the effect of statin on VF progression.[16,38] In the current study, although patients using statins did have more comorbidities, there were no significant difference in age, systolic and diastolic blood pressure, and most of the biochemistry tests except lipid profile between the two groups. We believe that the results of our analysis had reduced the interference of these factors.

There were several limitations of the current study. First, the retrospective nature of the study may have introduced selection or information bias. Second, the sample size was relatively small. Third, the current study only evaluated the impact on VF but not on optical coherence tomography. Whether the use of statins would affect the structural changes of the optic disc remains to be addressed. Fourth, although statistically insignificant, the statin group had worse baseline MD. However, the MD in both groups were within the range of 0 to -6 which was classified as mild glaucoma according to the Glaucoma Staging System. The difference would not affect the result.[39]

5. Conclusion

The current study was the first analyzing the long-term effect of oral statin on glaucoma visual field progression. We found that statin use did not affect the global rates of VF progression. However, in subfield analysis, the progression in the superonasal VF was significantly slower in statin users than in non-statin users. The protective effect of statins against VF progression might be regional but not to the entire visual field. Whether statin use slow the progression of glaucoma still needs further elucidation.

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Conflict of interest

No conflicting relationship exists for any author.

References

1. Thylefors B, Négrel AD, Pararajasegaram R, et al. Global data on blindness. *Bull World Health Organ.* 1995;73:115–121.
2. Friedman DS, Wolfs RC, O'Colmain BJ, et al. Prevalence of open-angle glaucoma among adults in the United States. *Arch Ophthalmol.* 2004; 122:532–538.
3. Wilson MR, Coleman AL, Yu F, et al. Functional status and well-being in patients with glaucoma as measured by the Medical Outcomes Study Short Form-36 questionnaire. *Ophthalmology.* 1998;105:2112–2116.
4. Parrish RK 2nd, Gedde SJ, Scott IU, et al. Visual function and quality of life among patients with glaucoma. *Arch Ophthalmol.* 1997;115:1447–1455.
5. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005;366:1267–1278.
6. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006;355: 549–559.
7. Zacco A, Togo J, Spence K, et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors protect cortical neurons from excitotoxicity. *J Neurosci.* 2003;23:11104–11111.
8. Vaughan CJ, Delanty N. Neuroprotective properties of statins in cerebral ischemia and stroke. *Stroke.* 1999;30:1969–1973.
9. 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.
10. Krempler K, Schmeer CW, Isenmann S, et al. Simvastatin improves retinal ganglion cell survival and spatial vision after acute retinal ischemia/reperfusion in mice. *Invest Ophthalmol Vis Sci.* 2011;52:2606–2618.
11. Talwar N, Musch DC, Stein JD. Association of daily dosage and type of statin agent with risk of open-angle glaucoma. *JAMA Ophthalmol.* 2017; 135:263–267.
12. Stein JD, Newman-Casey PA, Talwar N, et al. The relationship between statin use and open-angle glaucoma. *Ophthalmology.* 2012;119:2074–2081.
13. 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.
14. Chen HY, Hsu SY, Chang YC, et al. Association between statin use and open-angle glaucoma in hyperlipidemia patients: A Taiwanese population-based case-control study. *Medicine (Baltimore).* 2015;94:e2018.
15. 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.
16. Leung DY, Li FC, Kwong YY, et al. Simvastatin and disease stabilization in normal tension glaucoma: a cohort study. *Ophthalmology.* 2010;117: 471–476.
17. Whigham B, Oddone EZ, Woolson S, et al. The influence of oral statin medications on progression of glaucomatous visual field loss: A propen-

sity score analysis. *Ophthalmic Epidemiol.* 2018;25:207–214.
18. Baez KA, McNaught AI, Dowler JG, et al. Motion detection threshold and field progression in normal tension glaucoma. *Br J Ophthalmol.* 1995;79: 125–128.
19. Bhandari A, Crabb DP, Poinoosawmy D, et al. Effect of surgery on visual field progression in normal-tension glaucoma. *Ophthalmology.* 1997; 104:1131–1137.
20. Aung T, Oen FT, Wong HT, et al. Randomised controlled trial comparing the effect of brimonidine and timolol on visual field loss after acute primary angle closure. *Br J Ophthalmol.* 2004;88:88–94.
21. Nouri-Mahdavi K, Caprioli J, Coleman AL, et al. Pointwise linear regression for evaluation of visual field outcomes and comparison with the advanced glaucoma intervention study methods. *Arch Ophthalmol.* 2005; 123:193–199.
22. Jonas JB, Martus P, Horn FK, et al. Predictive factors of the optic nerve head for development or progression of glaucomatous visual field loss. *Invest Ophthalmol Vis Sci.* 2004;45:2613–2618.
23. Kang JH, Boumenna T, Stein JD, et al. Association of statin use and high serum cholesterol levels with risk of primary open-angle glaucoma. *JAMA Ophthalmol.* 2019;137:756–765.
24. Owen CG, Carey IM, Shah S, et al. Hypotensive medication, statins, and the risk of glaucoma. *Invest Ophthalmol Vis Sci.* 2010;51:3524–3530.
25. Preiss D. Do statins reduce microvascular complications in diabetes? *Lancet Diabetes Endocrinol.* 2014;2:858–859.
26. Goldfine AB. Statins: is it really time to reassess benefits and risks? *N Engl J Med.* 2012;366:1752–1755.
27. Sabanayagam C, Liew G, Tai ES, et al. Relationship between glycated haemoglobin and microvascular complications: is there a natural cut-off point for the diagnosis of diabetes? *Diabetologia.* 2009;52:1279–1289.
28. Ridker PM, Pradhan A, MacFadyen JG, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet.* 2012;380:565–571.
29. Cenedella RJ, Kuszak JR, Al-Ghoul KJ, et al. Discordant expression of the sterol pathway in lens underlies simvastatin-induced cataracts in Chbb. *J Lipid Res*. 2003;44:198–211.
30. Hartman HA, Myers LA, Evans M, et al. The safety evaluation of fluvastatin, an HMG-CoA reductase inhibitor, in beagle dogs and rhesus monkeys. *Fundam Appl Toxicol.* 1996;29:48–62.
31. AREDS2 Research Group, Al-Holou SN, Tucker WR, et al. The association of statin use with cataract progression and cataract surgery: The AREDS2 Report Number 8. *Ophthalmology.* 2016;123:916–917.
32. Erie JC, Pueringer MR, Brue SM, et al. Statin use and incident cataract surgery: A case-control study. *Ophthalmic Epidemiol.* 2016;23:40–45.
33. Zink JM, Grunwald JE, Piltz-Seymour J, et al. Association between lower optic nerve laser Doppler blood volume measurements and glaucomatous visual field progression. *Br J Ophthalmol.* 2003;87:1487–1491.
34. Kim JM, Kyung H, Shim SH, et al. Location of initial visual field defects in glaucoma and their modes of deterioration. *Invest Ophthalmol Vis Sci.* 2015;56:7956–7962.
35. Hernández-Perera O, Pérez-Sala D, Navarro-Antolín J, et al. Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. *J Clin Invest.* 1998;101: 2711–2719.
36. Nagaoka T, Takahashi A, Sato E, et al. Effect of systemic administration of simvastatin on retinal circulation. *Arch Ophthalmol.* 2006;124:665–670.
37. Terai N, Spoerl E, Fischer S, et al. Statins affect ocular microcirculation in patients with hypercholesterolaemia. *Acta Ophthalmol.* 2011;89:e500–e504.
38. Newman-Casey PA, Talwar N, Nan B, et al. The relationship between components of metabolic syndrome and open-angle glaucoma. *Ophthalmology.* 2011;118:1318–1326.
39. Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. *Am J Ophthalmol.* 2006;141: 24–30.