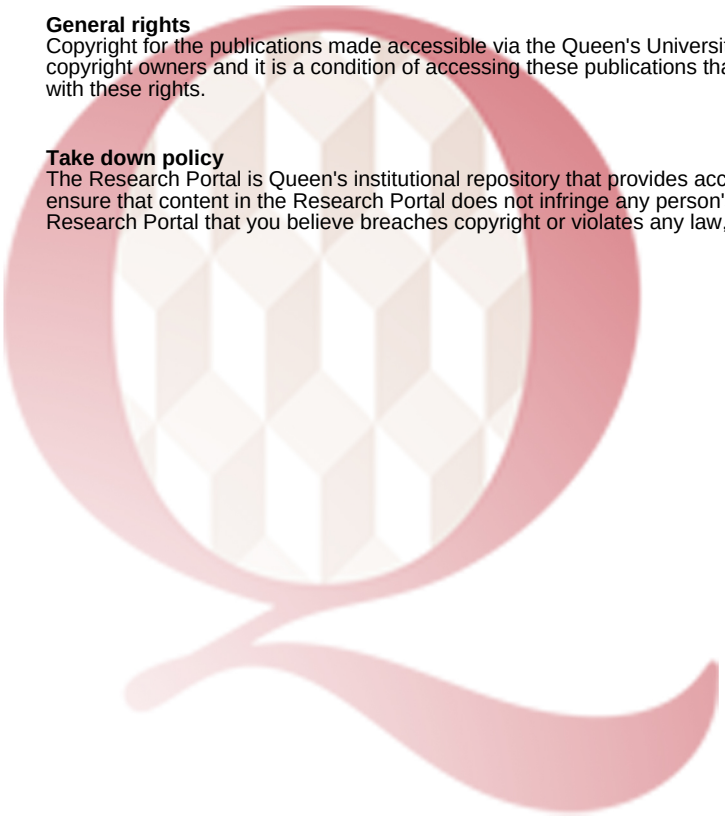
The effect of statins on intraocular pressure and on the incidence and progression of glaucoma: A Systematic Review and Meta-analysis

McCann, P., Hogg, R. E., Fallis, R., & Azuara-Blanco, A. (2016). The effect of statins on intraocular pressure and on the incidence and progression of glaucoma: A Systematic Review and Meta-analysis. Investigative Opthalmology and Visual Science, 57(6), 2729-2748. DOI: 10.1167/iovs.15-18595

Published in:
Investigative Opthalmology and Visual Science

Document Version:
Publisher's PDF, also known as Version of record



The Effect of Statins on Intraocular Pressure and on the Incidence and Progression of Glaucoma: A Systematic Review and Meta-Analysis

Paul McCann,[1] Ruth E. Hogg,[1] Richard Fallis,[2] and Augusto Azuara-Blanco[1]

[1]Centre for Experimental Medicine, Queens University Belfast, Belfast, United Kingdom
[2]Medical Library, Queen's University Belfast, Belfast, United Kingdom

Correspondence: Paul McCann, Centre for Experimental Medicine, School of Medicine, Dentistry & Biomedical Sciences, Queen's University Belfast, Institute of Clinical Science, Block A, Grosvenor Road, Belfast BT12 6BA, Northern Ireland, UK;
pmccann45@qub.ac.uk.

Submitted: November 5, 2015
Accepted: April 14, 2016

Citation: McCann P, Hogg RE, Fallis R, Azuara-Blanco A. The effect of statins on intraocular pressure and on the incidence and progression of glaucoma: a systematic review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2016;57:2729–2748. DOI:10.1167/iovs.15-18595

Purpose. We conducted a systematic review and meta-analysis of observational studies to evaluate the effect of oral statins on intraocular pressure (IOP) and the incidence and progression of glaucoma.

Methods. This was a systematic review of the literature and meta-analysis. Searches of PubMed/Medline and Embase were conducted to include all types of studies. Gray literature abstracts were also considered for inclusion. Last search date was February 2016. Risk of bias was assessed using the Newcastle-Ottawa scale independently by two reviewers. Odds ratios (OR) or hazard ratios (HR) and 95% confidence intervals (CI) were extracted from each study. Pooled ORs for incidence of glaucoma were calculated using a random-effects model.

Results. We identified seven cohort studies, three case–control studies, and one cross-sectional study with a total number of 583,615 participants. No randomized controlled trials were retrieved. Pooled ORs demonstrated a statistically significant association between short-term statin use ($\leq$2 years) and reduced incidence of glaucoma (OR 0.96, 95%CI 0.94, 0.99). Pooled ORs of long-term statin use (>2 years) did not demonstrate statistically significant reduction in incidence of glaucoma (OR 0.70, 95%CI 0.46, 1.06). There was inconsistent evidence for the protective effect of statins against the progression of glaucoma, although there was no standard definition for progression across studies. There was no significant difference in IOP associated with statin use.

Conclusions. Short-term statin use is associated with a reduced incidence of glaucoma. The effect of statins on glaucoma progression and IOP is uncertain.

Keywords: glaucoma, statins, incidence, progression, intraocular pressure

Glaucoma is a progressive optic neuropathy characterized by structural optic nerve head changes and visual field loss. The leading cause of irreversible blindness worldwide, glaucoma affects 64.3 million people, and this is expected to increase to 111.8 million by 2040.[1] The global prevalence of open-angle glaucoma (OAG) between 40 and 80 years is estimated at 3.54% worldwide.[1,2]

Major risk factors for OAG include age and intraocular pressure (IOP).[3] Intraocular pressure is currently the only modifiable major risk factor for OAG development and progression.[4] Medical and surgical therapies have been successfully introduced that lower IOP by reducing aqueous production and increasing outflow; however, these therapies are not without adverse effects. Furthermore, it is not uncommon for the disease to progress despite successful IOP reduction.[5] Therefore demand continues for the discovery of novel therapeutic agents that offer patients protection from the onset and progression of glaucomatous visual loss.

During development pipelines, 90% of drug candidates fail at some point, leaving only 10% as a marketable product.[6] Failure late in clinical development results in greater amounts of time, money, and effort invested with little or no return. Drug repurposing is a process of finding new uses for drugs outside the scope of the original indication.[7] This benefits from reduced risk and costs because the drug candidates have either already been approved for clinical use or been through several stages of clinical development with known safety and pharmacokinetic profiles.[8]

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is a rate-limiting enzyme necessary for the production of the intermediate product L-mevalonate in the biosynthetic pathway of cholesterol.[9] Statins are a relatively well tolerated class of cholesterol-lowering medication commonly prescribed in patients with dyslipidemia for the primary and secondary prevention of cerebrovascular and cardiovascular disease. Clinical and scientific evidence suggests that statins are capable of reducing the risk of cerebrovascular and cardiovascular disease independent of their effect on cholesterol levels.[10,11] The so-called pleiotropic properties of statins such as inhibition of isoprenylation of Rho-GTPase[12] and immunomodulation[13] have been proposed to protect retinal ganglion cells (RGCs) against glaucomatous damage.[14] Thus there has been increasing interest in the potential role of statins in glaucoma pathologic mechanisms and therapeutics.[15]

The purpose of this literature review is to examine the current clinical and epidemiologic evidence investigating the strength and consistency of the association between clinical

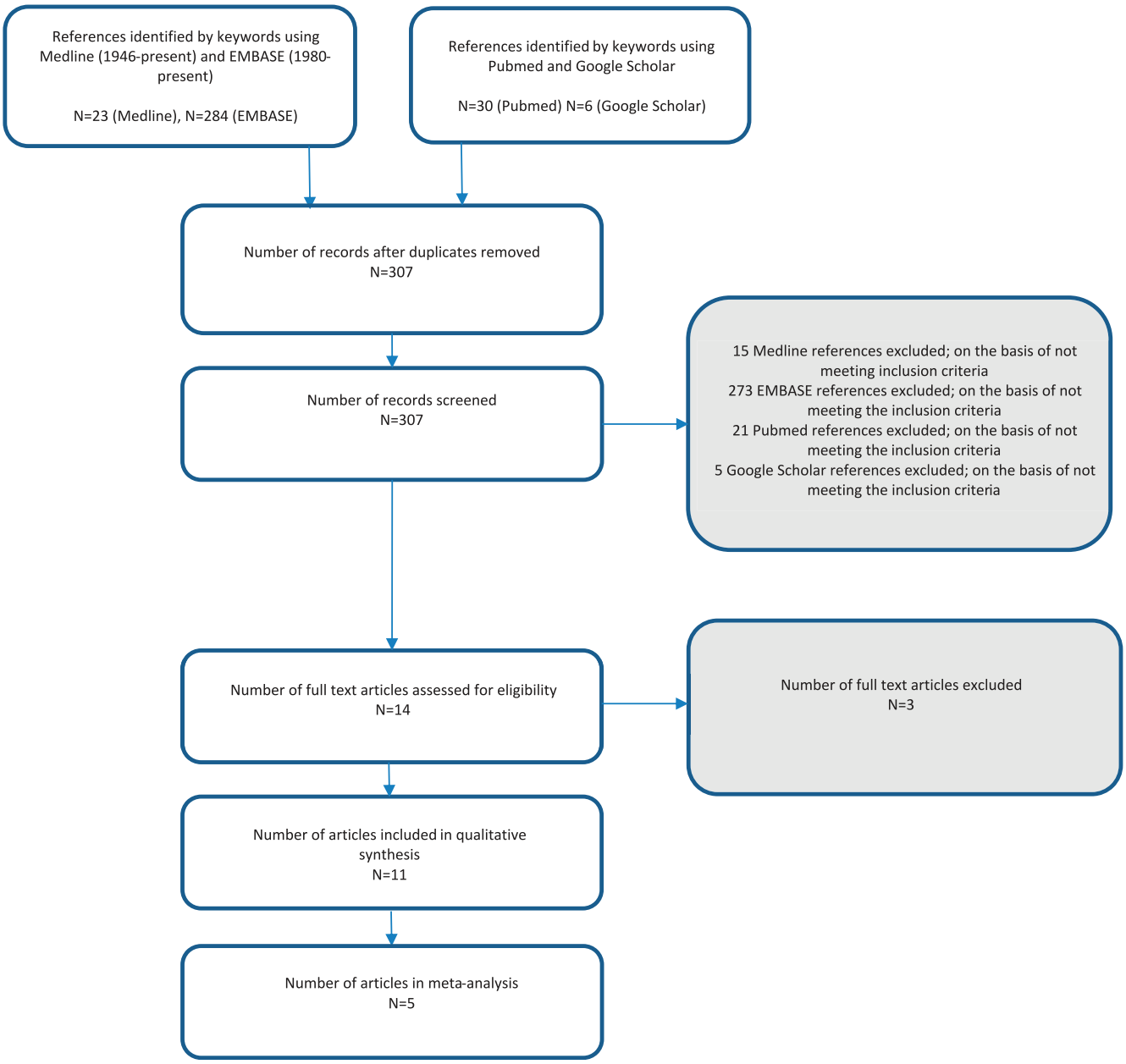


Figure 1. Search strategy flow diagram.

statin use and the incidence or progression of glaucoma and its effects on IOP.

Methods

We followed the MOOSE guidelines[16] and registered our review at PROSPERO International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO, registration no: CRD42015014875). This article adheres to the PRISMA statement[17] checklist for the preferred reporting of systematic reviews and meta-analysis.

Eligibility Criteria for Considering Studies for This Review

This systematic review focused on studies that investigated the association between statin use and glaucoma incidence or progression and the effect on IOP. Included studies were limited to primary research; however, they were not limited by design, sample size, participants, follow-up, or primary outcome measures.

Search Methods for Identifying Studies

Medline (1946-February week 3 2016) and Embase (1980-2016 week 8) were searched on 24 February, 2016 (Fig. 1). The search strategy used subject headings in both databases: MeSH terms in Medline and Emtree terms in Embase (Appendix 1). PubMed and Google Scholar searches were also conducted using the search terms "glaucoma" and "statins" to pick up any articles that had not been added to Medline yet. The search strategies were limited to human studies and English language. Included studies were limited to published studies to the exclusion of editorials, commentaries, and article summaries.

Reference lists of articles were also interrogated for additional relevant papers. Abstracts were also included.

Study Selection

Two authors (REH and PM) screened all titles and abstracts generated from the searches to find studies that contained information on the topic of interest. Full articles were retrieved for detailed assessment by two authors, and papers that did not meet the inclusion criteria were excluded.

Data Collection

Each study was characterized by extracting methodological details onto a predesigned form by two independent reviewers.[18] Relevant outcomes and results were extracted into another form and were screened for comparability. When there were inconsistencies between reviewers' opinions, there were further discussions until consensus was reached. In studies in which more than one estimate of effect was presented, agreement was reached about the most appropriate "adjusted" estimate to include. Attempts were made to contact authors by e-mail when papers presented insufficient data.

Risk of Bias Assessment

Risk of bias in the nonrandomized observational studies was assessed using Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort and case–control studies as outlined in *The Cochrane Handbook of Systematic Reviews*.[18] The NOS includes a star system in which a study is judged on three domains (Appendix 2); representativeness of study group selection (four items), comparability of groups (two items), and ascertainment of either the exposure or outcome in case–control studies or cohort studies (three items). Studies score a star for each item addressed with a score ranging from 0 to 9. Those studies scoring greater than 7 were distinguished from scores $\leq$7 as having a lower risk of bias. The cutoff of 7 was used as it had been adopted by a previous review.[19] Two independent reviewers repeated this process, and inconsistencies were discussed until consensus was reached. When insufficient information was available to ascertain the NOS score, attempts were made to contact authors for further details.

Data Synthesis and Analysis

Statistical analysis and meta-analysis were performed using RevMan 5.3 software (The Cochrane Collaboration, Copenhagen, Denmark). We combined the results of different study designs in the meta-analysis because we used the "rare disease assumption" that odds ratios (OR) and risk ratios can be considered equivalent when the disease has a prevalence less than 5%.[20,21] The χ^2 test of between-study heterogeneity was used to test the null hypothesis that the underlying treatment effect of statins is identical in all studies. The test statistic, Q, follows a χ^2 distribution with the degrees of freedom equal to the number of studies minus 1. The I^2 statistic measured the degree of inconsistency in the observed treatment effect of statins by measuring the percentage of total variation across the studies that is due to heterogeneity rather than chance. Forest plots were used to graphically represent the investigation of heterogeneity. Within the forest plots, estimates were stratified into subgroups on the basis of length of exposure to statins ($\leq$2 and $>$2 years) because the primary studies made these stratifications. Overall effect size was then determined for each of the subgroups. A further meta-analysis was performed on estimates that were not subgrouped by length of exposure to statins. We used the most conservative of the two effects models, random effects, to estimate the pooled effect size. This takes into account extra variations when assuming that the studies are estimating different underlying treatment effects. Publication bias was checked for using funnel plots. Sensitivity analysis was performed to examine the impact of poor-quality studies upon the meta-analysis. For the purposes of the description of the results, study outcomes were classified into the three domains relevant to glaucoma: incidence, progression, and IOP.

Results

The initial searches identified 307 records after the removal of duplicates (Fig. 1). Following screening of these 307 records, 293 were excluded due to being either irrelevant or non-epidemiologic studies. Full texts of 14 potentially relevant manuscripts were retrieved. Three were excluded due to being editorials, commentaries, or summaries of other included studies. The remaining 11 studies explored the association between primary OAG and statin use and were included. Of these 11 studies, 9 were full studies and 2 were abstracts. No randomized controlled trials were retrieved. Four studies investigated glaucoma incidence, one study investigated both glaucoma incidence and progression, and five other studies investigated glaucoma progression. The effect of statin therapy on IOP was reported in three studies. The publication dates for all the studies ranged between 2004 and 2015.

Descriptions of populations, sample sizes, and outcome measures are outlined in Table 1 and the design for each study is defined in Table 2. The definition of the glaucoma-related outcome measure, the method of ascertainment of statin exposure, and the estimated effects of statins on incidence, progression, and IOP for each included study are presented in Tables 3 to 5, respectively.

Risk of Bias Assessment

Using the NOS, six cohort studies were judged to score $\geq$8 and the remaining two cohort studies were judged to score $\leq$7 in quality (Table 6). The lowest-scoring cohort studies were from the two gray literature abstracts with scores of 5 and 0 out of 9. One case–control study was judged to score $\geq$8 on the NOS, and the other two were judged to have scored $\leq$7 (Table 7).

Statin Use and Incidence of Glaucoma

The association between statin use and incidence of glaucoma was examined in five studies: two nested case–control studies, one case–control study, one retrospective cohort study, and one prospective cohort study. The outcomes for each study were stratified by the length of exposure to statins as per the primary studies and were then outlined in forest plots (Figs. 2, 3). A further meta-analysis was performed on outcomes reported from studies that did not stratify by the length of exposure (Fig. 4). Overall estimates for incidence of glaucoma were presented in forest plots. For exposure to statins for $\leq$2 years, overall estimated OR was 0.96 (95%CI [confidence interval] 0.94, 0.99) and for $>$2 years, overall estimate OR was 0.70 (95%CI 0.46, 1.06). Meta-analysis of outcomes that were not stratified by length of exposure did not show a statistically significant reduction in the incidence of OAG (OR 0.94, 95%CI 0.83, 1.06).

Among studies evaluating the short-term use of statins, McGwin et al.,[22] Owen et al.,[23] and Stein et al.[24] used diagnostic read codes to define glaucoma incidence, whereas Marcus et al.[25] used a clinical diagnosis. McGwin et al.[22] were

Table 1. List of Features of All Included Studies

Author	Design	Dataset (Country)	Population
McGwin et al.,[22] 2004	Nested case–control study	Veterans Affairs Medical Center (US)	All male patients, 50 y or older, who had at least 1 visit to BVAMC hospital between January 1, 1997 and December 31, 2001
De et al. 2006, abstract	Retrospective cohort study	University of California, San Francisco (UCSF), and the San Francisco Veterans Affairs Medical Center (US) retrospective chart review	Patients with OAG
De Castro et al.,[27] 2007	Retrospective cohort study	OAG suspects at the Beckman Vision Center (BVC), UCSF (US)	Glaucoma suspects at BVC UCSF from January 2001 to June 2006
Tong,[28] 2008, abstract	Retrospective cohort study	n.r.	n.r.
Iskedjian et al.,[29] 2009	Retrospective cohort study	RAMQ database repository of prescription claims (Canada)	Random sample from 75% of 2.7 million plan recipients
Leung et al.,[30] 2010	Prospective cohort study	Hong Kong Eye Hospital (Hong Kong)	Prospectively recruited cohort of patients from Hong Kong Eye Hospital
Owen et al.,[23] 2010	Nested case–control study	177 practices in DIN-LINK UK primary care database (UK)	Patients in DIN-LINK database of primary care records with minimum of 5-y continuous high-quality records
Marcus et al.,[25] 2012	Prospective cohort study	Rotterdam Study (The Netherlands)	Participants of the Rotterdam Study n = 7983
Stein et al.,[24] 2012	Retrospective cohort study	i3 InVision Data Mart database; beneficiaries in a managed care network throughout the United States (US)	Beneficiaries who received any form of eye care from 2001 to 2009 n = 10,326,832
Khawaja et al.,[31] 2014	Cross-sectional study, within cohort study	EPIC-Norfolk eye study (UK)	EPIC study participants n = 8623
Chen et al.,[26] 2015	Case–control study	National Health Insurance program (Taiwan)	Longitudinal Health Insurance Database (LHID)

A, atorvastatin; A/ab, atorvastatin and amlodipine besylate; C, cerivastatin; F, fluvastatin; FU, follow-up; GAT, Goldmann applanation tonometry; L, lovastatin; Ln, niacin and lovastatin; n.r., not reported; ORA, ocular response analyzer; POAG, primary open-angle glaucoma; PGA, prostaglandin analogue; P, pravastatin; P/ba, pravastatin and buffered aspirin; R, rosuvastatin; S, simvastatin. BVAMC, Birmingham Veterans Affairs Medical Center; EPIC, European Prospective Investigation into Cancer; HFA, Humphreys Field Analyser; NTG, Normal Tension Glaucoma; RAMQ, Regie de l'assurance malaide du Quebec; Se, Simvastatin and ezetimibe.

1, age; 2, sex; 3, diabetes; 4, lipid metabolism disorders; 5, hypertension; 6, cardiovascular disease (ischemic heart disease); 7, cerebrovascular disease; 8, arterial disease; 9, disc hemorrhages; 10, asthma; 11, chronic obstructive pulmonary disease; 12, IOP; 13, myopia; 14, family history of glaucoma; 15, NSCLD use; 16, concomitant medications; 17, race; 18, obesity; 19, hypotension; 20, sleep apnea; 21, migraine; 22, ocular comorbidities; 23, education level; 24, body mass index; 25, central corneal thickness; 26, cancer; 27, hypothyroidism; 28, autoimmune disease; 29, vasculitis; 30, depression; 31, Charlson comorbidity index; 32, frequency of eye care visits.

Table 1. Extended

Author	Sample Size	Age	Females	Study Duration, Follow-Up	Statin Types
McGwin et al.,[22] 2004	667 cases and 6667 controls	≥50 y	0%	January 1, 1997 to December 31, 2001	A, C, F, P, S, L
De et al. 2006, abstract	315 patients; numbers in exposed and control groups not reported	n.r.	n.r.	n.r.	n.r.
De Castro et al.,[27] 2007	76 patients, 149 eyes	11–85 y	64.5%	January 2001 to June 2006 Statin-only group mean FU 26.8 ± 10.7 mo Statin and aspirin group mean FU 30.8 ± 14.2 mo Control group mean FU 28.3 ± 11.5 mo	n.r.
Tong,[28] 2008, abstract	353 patients with normal-tension glaucoma; numbers in exposed and control groups not reported	n.r.	n.r.	n.r.	n.r.
Iskedjian et al.,[29] 2009	8548 patients	<20–≥80 y Mean age 70.5	59%	January 1, 2001 to March 1, 2005	n.r.
Leung et al.,[30] 2010	256 patients with NTG, 256 eyes following 1 exclusion	18 y or older	35.5% of those taking statins 46.2% of those not taking statins	36 mo	S
Owen et al.,[23] 2010	17,556 individuals; 8778 cases and 8778 controls	40–90 y Mean age 70	53%	5 y	S, P, F, A, C, R
Marcus et al.,[25] 2012	3939 participants who did not have OAG at baseline	≥55 y	49.1% incident POAG 58% no incident POAG 56.6% of cholesterol-lowering drug users 58.9% nonusers of cholesterol-lowering drugs	Mean follow-up 9.8 y Incident POAG: follow-up ended at first visit with glaucomatous visual field loss Without incident POAG: follow-up was from baseline to last visit with reliable perimetry	S, P, F, A, C, R
Stein et al.,[24] 2012	524,109 persons with ≥1 diagnosis of hyperlipidemia	60 y or older	56.5% of beneficiaries who did not develop OAG 56.0% of beneficiaries who developed OAG	January 1, 2001 to December 31, 2009	L, Ln C, A A/ab, R, F, P, P/ba, S, Se
Khawaja et al.,[31] 2014	7093 participants following exclusion criteria	48–92 y Mean age 68 y	56%	2004–2011	n.r.
Chen et al.,[26] 2015	1276 cases, 12,760 controls	Mean age 64.1 y	49.5%	2004–2011	S, L, P, F, A, R

unable to demonstrate a statistically significant effect of statin use for less than 12 months (OR 1.03, 95%CI 0.77, 1.39) or for 12 to 23 months (OR 0.75, 95%CI 0.46, 1.23). Consistent with this result, Owen et al.[23] did not find a significant association between short-term statin use and glaucoma incidence when adjusted for a socioeconomic index, comorbidities, and other medications taken (OR 0.98, 95%CI 0.89, 1.08). Marcus et al.[25] were unable to demonstrate a statistically significant protective effect of cumulative statin use for less than 2 years (hazard ratio [HR] 0.89, 95%CI 0.41, 1.94). However, Stein et al.[24] found statistically significant protective effects of statin use for 1 year using two parameters of glaucoma incidence: OAG onset from no previous diagnosis (HR 0.960, 95%CI 0.933, 0.988) and incidence of medical treatment for OAG (HR 0.950, 95%CI 0.924, 0.976).

Regarding the long-term use of statins, three studies reported an association with reduced OAG incidence. McGwin et al.[22] and Stein et al.[24] used diagnostic read codes to define

Table 1. Extended

Author	Confounders Adjusted For	Outcomes Measured
McGwin et al.,[22] 2004	1, 3, 4, 5, 6, 7, 8	1) Statin use, yes/no: OR of glaucoma incidence associated with statin use 2) Statin use, current/past: OR of glaucoma incidence associated with current or past statin use 3) Statin use, <12 mo, 12–23 mo, >23 mo: OR of glaucoma incidence associated with statin use, stratified by length of treatment
De et al. 2006, abstract	n.r.	1) Mean deviation: mean change per year 2) Pattern standard deviation: mean change per year
De Castro et al.,[27] 2007	1, 2, 17, 12, 25, 13, 5, 3, 21, 26, 4, 27, 28, 7, 8, 29	1) Visual field progression: glaucoma hemifield test (HFA) 2) Mean change in optic nerve parameters: confocal laser ophthalmoscopy (CLSO): Heidelberg Retinal Tomograph II
Tong,[28] 2008, abstract	1, 12, 25, all not adjusted for	1) Association of statins with stable disease: univariate analysis
Iskedjian et al.,[29] 2009	1, 2	1) Proportion of glaucoma patients requiring adjunctive glaucoma therapy within 12 mo of starting PGA therapy dependent upon systemic medication (statin) use
Leung et al.,[30] 2010	1, 7, 9	1) Visual field progression with HFA perimetry 2) IOP: GAT
Owen et al.,[23] 2010	1, 2, 3, 6	1) Any statin prescription in 5 y before glaucoma diagnosis date, % of cases with statin prescription versus % of controls with statin prescription 2) OR of statin treatment in cases (glaucoma) compared with controls
Marcus et al.,[25] 2012	1, 2, 12, 13, 14, 15	1) HR of glaucoma incidence in statin exposure a) Cumulative use for less than 2 y b) Cumulative use for more than 2 y 2) IOP at follow-up (GAT) associated with statin use, adjusted for IOP-lowering treatment at follow-up
Stein et al.,[24] 2012	1, 2, 3, 5, 15, 16, 17, 18, 19, 20, 21, 22, 23	1) Incidence of OAG from no previous diagnosis 2) Progression from glaucoma suspect to OAG 3) Need for medical intervention for OAG 4) Need for surgical intervention for OAG
Khawaja et al.,[31] 2014	1, 2, 24	1) IOP (ORA): mean Goldmann correlated IOP and association with statin use
Chen et al.,[26] 2015	3, 5, 15, 30, 31, 32	1) Statin exposure, yes/no: OR of glaucoma incidence associated with statin exposure 2) Statin exposure: none, <30, 30–119, ≥120 defined daily doses per year

OAG incidence, whereas Marcus et al.[25] used a clinical diagnosis. McGwin et al.[22] demonstrated a statistically significant association between incidence of glaucoma and statin use for greater than 23 months (OR 0.60, 95%CI 0.39, 0.92). In support of this, Marcus et al.[25] demonstrated a statistically significant protective effect of cumulative statin use for more than 2 years (HR 0.46, 95%CI 0.23, 0.94). Finally, Stein et al.[24] found statistically significant protective effects of statin use for 2 years using OAG onset from no previous diagnosis (HR 0.922, 95%CI 0.870, 0.976) and incidence of medical treatment for OAG (HR 0.902, 95%CI 0.854, 0.953).

Our meta-analysis suggests that statin therapy for ≤2 years confers a 4% reduction in the incidence of OAG (Fig. 2) while statin therapy for >2 years did not confer a statistically significant reduction in the incidence of OAG (Fig. 3). Statin use not stratified by length of exposure to statins also did not confer a statistically significant reduction in the incidence of OAG (Fig. 4).

Table 2. List of Study Design Features

	McGwin et al.,[22] 2004	De et al. 2006	De Castro et al.,[27] 2007	Tong,[28] 2008	Iskedjian et al.[29] 2009	Leung et al.,[30] 2010	Owen et al.,[30] 2010	Marcus et al.,[25] 2012	Stein et al.,[24] 2012	Khawaja et al.,[31] 2014	Chen et al.,[26] 2015
Was there a comparison:											
Between 2 or more groups of participants receiving different interventions?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Within the same group of participants over time?	N	N	N	N	N	N	N	N	N	N	N
Were participants allocated to groups by:											
Concealed randomization?	N	N	N	N	N	N	N	N	N	N	N
Quasi-randomization?	N	N	N	N	N	N	N	N	N	N	N
By other action of researchers?	N	N	N	N	N	N	N	N	N	N	N
Time differences?	N	N	N	N	N	N	N	N	N	N	N
Location differences?	n/a	N	N	N	N	Y	N	N	N	N	n/a
Treatment decisions?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Participants' preferences?	N	N	N	N	N	N	N	N	N	N	N
On the basis of outcome?	N	N	N	N	N	N	N	N	N	N	Y
Some other process? Specify	Nonglaucomatous indications for statin therapy (all studies)										
Which parts of the study were prospective:											
Identification of participants?	Y	N	N	N	N	Y	N	Y	N	Y	N
Assessment of baseline and allocation to intervention?	Y	N	N	N	N	Y	N	Y	N	Y	N
Assessment of outcomes?	Y	N	Y	N	N	Y	N	Y	N	Y	N
Generation of hypothesis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
On what variables was comparability between groups assessed:											
Potential confounders?	Y	n.r.	Y	Y	Y	Y	Y	Y	Y	Y	Y
Baseline assessment of outcome variables?	N	n.r.	Y	N	Y	Y	N	Y	Y	N	N
Study design	Nested case–control study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Prospective cohort study	Case–control study	Prospective cohort study	Retrospective cohort study	Cross-sectional study within cohort study	Case–control study

n/a, not applicable; N, no; n.r., not reported; Y, yes.

Table 3. Features and Results of Studies Investigating Association Between Statin Use and Glaucoma Incidence

Author	Glaucoma Incidence Definition	Method Used to Quantify Statin Use	Statin Use Definition	Summary of Statin-Related Primary Outcomes in Glaucoma
McGwin et al.,[22] 2004	ICD-9-CM diagnostic codes; date first coded taken as diagnosis date, prevalent cases excluded	BVAMC prescription file queried: length of time between initial statin prescription and incidence of glaucoma extracted from the prescription file	<12 mo: 10.2% of cases <12 mo: 7.6% of controls 12–23 mo: 3.2% of cases 12–23 mo: 2.9% of controls >23 mo: 4.5% of cases >23 mo: 4.6% of controls	Adjusted glaucoma risk OR 1.03, 95%CI 0.77, 1.39 Adjusted glaucoma risk OR 0.75, 95%CI 0.46, 1.23 Adjusted glaucoma risk OR 0.60, 95%CI 0.39, 0.92 Statin use, yes; adjusted glaucoma risk OR 0.85, 95%CI 0.66, 1.09 Statin use, current; adjusted glaucoma risk OR 0.94, 95%CI 0.70, 1.27 Statin use, past; adjusted glaucoma risk OR 0.74, 95%CI 0.53, 1.04 Glaucoma risk OR in those taking statins adjusted for following individual medical conditions: a) Lipid metabolism disorders, yes; 0.63, 95%CI 0.41, 0.99 b) Cardiovascular disease, yes; 0.63 95%CI 0.42, 0.97 c) Cerebrovascular disease, no; 0.76, 95%CI 0.58, 0.99
Owen et al.,[30] 2010	DIN-LINK read codes for glaucoma diagnosis and prescriptions for glaucoma and ocular hypertension treatment; date first coded taken as diagnosis date	DIN-LINK database electronic search for oral statin prescription; within the 5 y previous to glaucoma diagnosis, number of days covered by prescription were estimated using amount prescribed and dosage instructions coded	Mean number of days statin coverage in 5-y study period: Cases: mean statin use 153.8 d Controls: mean statin use 150.9 d	Any statin prescription in 5 y before glaucoma diagnosis date; cases, glaucoma 19.6% versus controls 18.7% $P < 0.001$ Adjusted OR for presence of statin in glaucoma cases compared to controls; 2 y before diagnosis; 0.98 95%CI 0.89, 1.08 5 y before diagnosis; 0.97 95%CI 0.88, 1.06
Marcus et al.,[25] 2012	Diagnosis; no glaucomatous visual field loss at baseline and glaucomatous visual field loss in at least 1 eye at follow-up. OAG confirmed and secondary causes excluded by expert ophthalmologic assessment.	Automated pharmacy records; provided information on medication name, date of first prescription, and duration of use	No use Cumulative use for less than 2 y Cumulative use for more than 2 y Median length of statin use among statin users: 1424 d	Incidence; 108 of 3939 eligible participants developed OAG, 2.7% Cumulative use for less than 2 y; HR 0.89, 95%CI 0.41, 1.94 $P = 0.77$ Cumulative use for more than 2 y; HR 0.46, 95%CI 0.23, 0.94 $P = 0.033$ Statin use and glaucoma hazard ratio; HR 0.54, 95%CI 0.31, 0.96 $P = 0.034$

Table 3. Continued

Author	Glaucoma Incidence Definition	Method Used to Quantify Statin Use	Statin Use Definition	Summary of Statin-Related Primary Outcomes in Glaucoma
Stein et al.,[24] 2012	ICD-9-CM diagnostic codes; OAG onset, from no previous diagnosis; incidence of medical treatment for OAG	Comprehensive pharmacy records database including number of days for which each participant was prescribed statin	No use	Incidence; 10,266 individuals, 4.3% of beneficiaries eligible for new diagnosis of OAG analysis received ≥1 incident OAG diagnosis during their time in the medical plan
			Number of months statin use	Following adjustment for confounding factors, hazard of developing OAG decreased 0.3% for every additional month of statin use; HR 0.997, 95%CI 0.994, 0.999 $P = 0.0056$. Following adjustment for confounding factors, hazard of receiving medical therapy for OAG decreased 0.4% for every additional month of statin use, HR 0.996, 95%CI 0.993, 0.998 $P = 0.0002$.
			Continuous statin use for 1 y	Those who took statins for 1 y had 4% decreased hazard of developing OAG relative to those who did not receive statins, HR 0.960, 95%CI 0.933, 0.988. Those who took statins for 1 y had 5% decreased hazard of receiving medical therapy for OAG relative to those who did not receive statins, HR 0.950, 95%CI 0.924, 0.976.
			Continuous statin use for 2 y	Those who took statins for 2 y had 8% decreased hazard of developing OAG relative to those who did not receive statins, HR 0.922, 95%CI 0.870, 0.976. Those who took statins for 2 y had 10% decreased hazard of receiving medical therapy for OAG relative to those who did not receive statins, HR 0.902, 95%CI 0.854, 0.953.
			Mean number of days statin coverage 800 ± 621 (range, 1–3266) d; 96% used medication ≥30 d	
Chen et al.,[26] 2015	Glaucoma incidence; ICD-9-CM diagnostic codes for OAG diagnosis	Longitudinal Health Insurance Database (Taiwan) drug prescription registry	Duration from initial statin prescription date to index date, diagnosis date: no use; <30 defined daily doses/y; 30–119 defined daily doses/y; >120 defined daily doses/y	Statin use, yes; adjusted glaucoma risk OR 1.02, 95%CI 0.90, 1.15 <30 defined daily doses/y; adjusted glaucoma risk OR 0.87, 95%CI 0.73, 1.03 30–119 defined daily doses/y; adjusted glaucoma risk OR 1.03, 95%CI 0.88, 1.21 ≥120 defined daily doses/y; adjusted glaucoma risk OR 1.24, 95%CI 1.03, 1.49

BVAMC, Birmingham Veterans Affairs Medical Center.

Table 4. Features and Results of Studies Investigating Association Between Statin Use and Glaucoma Progression

Author	Glaucoma Progression Definition	Method Used to Quantify Statin Use	Statin Use Definition	Summary of Statin-Related Primary Outcomes in Glaucoma
De et al. 2006	Glaucoma progression; average change in mean deviation and pattern standard deviation per year	Retrospective chart review	Exposed: statins and/or aspirin use for greater than 23 mo Controls: patients with OAG who never used statins or aspirin or had used them for less than 23 mo	Average change in mean deviation per year between groups Statin users −0.476 dB/y $P = 0.3812$ Statin plus aspirin users −0.1338 dB/y $P = 0.3658$ Aspirin only 0.3381 dB/y $P = 0.7382$ Control 0.2774 dB/y overall $P = 0.59$ Change per year for pattern standard deviation was also not significantly different between the groups.
De Castro et al.,[27] 2007	Glaucoma progression; perimetric visual field, outside normal limits on glaucoma hemifield test; and confocal scanning laser ophthalmoscopy optic nerve head parameters—cup area, rim area, cup/disc area ratio, rim/disc area ratio, cup volume, rim volume, mean and maximum cup depth, height variation contour, cup shape measure, linear C:D, retinal nerve fiber layer (RNFL) cross-sectional area, mean global RNFL thickness (RNFLT), and temporal, superotemporal, inferotemporal, nasal, superonasal, and inferonasal RNFLT	Documented consistent use of statins and/or aspirin in medical records Each person interviewed over telephone to confirm medication use	Statin and/or aspirin use at any dose for greater than 23 mo. Medication use confirmed by telephone interview. Mean follow-up in statin group was 26.8 ± 10.7 mo.	No statistically significant differences among the number of patients who progressed to "outside normal limits" on glaucoma hemifield test in the statin group compared to controls Control group, 9 of 39, 23.1% patients progressed Statin-only group, 1 of 12, 8.33% patients progressed Aspirin-only group, 3 of 13, 23.1% patients progressed Statin + aspirin group, 2 of 12, 16.7% patients progressed $P = 0.833$ There were significant increases over time in rim volume, −13.7% controls, +26.7% statin only; $P = 0.0156$ RNFL cross-sectional area, −10.3% controls, +24.3% statin only; $P = 0.0051$; mean global RNFL thickness, −10.3% controls, +26.6% statin only; $P = 0.0114$ Supertemporal, inferotemporal, superonasal, and inferonasal RNFL thickness for the statin group and the statin plus aspirin group when compared to the controls. The statistically significant improvements in the statin and aspirin group were of less magnitude than in statin-only group.
Tong,[28] 2008	Glaucoma progression; mean deviation and pattern standard deviation	n.r.	n.r.	Statins associated with stable disease, univariate analysis Cramers V $P = 0.039$

Table 4. Continued

Author	Glaucoma Progression Definition	Method Used to Quantify Statin Use	Statin Use Definition	Summary of Statin-Related Primary Outcomes in Glaucoma
Iskedjian et al.,[29] 2009	Glaucoma progression; the proportion of prevalent glaucoma cases on PGA therapy, taking adjunctive glaucoma medical therapy stratified by systemic medication use including statins, identified by prescription database read codes Adjunctive therapy defined as any oral or topical therapy that has a primary indication for glaucoma including carbonic anhydrase inhibitors, miotics, mydriatics, and miscellaneous	Pharmaceutical records in prescription database read codes identified patients taking systemic medications including statins	Dispensed statin in at least 2 consecutive or nonconsecutive prostaglandin analogue intervals	No statistical difference in the proportion of patients initiating adjunctive glaucoma therapy in those using statins, 29.2%; $P = 0.076$ compared with those not taking systemic medications, 32.4% Statistically significant difference in the proportion of patients initiating adjunctive glaucoma therapy in those using statins in combination with antihypertensives, 25.2%; $P < 0.001$ compared with those not taking systemic medications, 32.4% Statistically significant difference in the proportion of patients initiating adjunctive glaucoma therapy in those using statins in combination with antihypertensives and antidiabetic medications, 21.8%; $P < 0.001$ compared with those not taking systemic medications, 32.4% Statistically significant difference in the proportion of patients initiating adjunctive glaucoma therapy in those using diuretics and at least 1 of the following medications: antihypertensives, antidiabetics, or statins, 24.5%; $P < 0.001$ compared with those not taking systemic medications, 32.4%
Leung et al.,[30] 2010	Glaucoma progression or stabilization by perimetry using Anderson criteria in prevalent normal-tension glaucoma cases	Systemic use of medications including statins, simvastatin only noted from computerized database	Statin use positive and statin use negative; continual statin use checked at each follow-up visit and verified by physician prescription and patient purchase	Simvastatin use was associated with visual field stabilization; statins were taken by 8/121 (6.6%) of patients who progressed and were taken by 23/135 (17%) of patients who remained stable $P = 0.011$. Logistic regression model with adjusting for history of disc hemorrhages, cerebrovascular disease, and age at baseline showed simvastatin use conferred a protective effect against visual field progression, RR 0.36; 95%CI 0.14, 0.91; $P = 0.030$.

Table 4. Continued

Author	Glaucoma Progression Definition	Method Used to Quantify Statin Use	Statin Use Definition	Summary of Statin-Related Primary Outcomes in Glaucoma
Stein et al.,[24] 2012	Glaucoma progression; ICD-9-CM diagnostic codes; Progression, from suspect OAG to OAG Surgical treatment for prevalent OAG	Comprehensive pharmacy records database including number of days for which each participant was prescribed statin	No use Number of months statin use Continuous statin use for 1 y Continuous statin use for 2 y Mean number of days statin coverage: 800 ± 621 (range, 1–3266) d 96% used medication ≥30 d	There were 6934 enrollees, 14.0% developed OAG among the 49,628 who had been diagnosed as OAG suspect during the look-back period. Following adjustment for confounding factors, hazard of progressing to OAG from OAG suspect decreased 0.4% for every additional month of statin use, HR 0.996, 95%CI 0.993, 0.999 $P = 0.0062$. Those who took statins for 1 y had 5% decreased hazard of progressing to OAG from OAG suspect relative to those who did not receive statins, HR 0.952, 95%CI 0.920, 0.986. Those who took statins for 2 y had 9% decreased hazard of progressing to OAG from OAG suspect relative to those who did not receive statins, HR 0.907, 95%CI 0.846, 0.973. Among the 8236 enrollees with incident OAG who had no glaucoma surgical intervention coded before their incident diagnosis of OAG, 1009, 12.3%, went on to require laser or incisional glaucoma surgery during their time on the plan. Following adjustment for confounding factors, hazard of an individual with OAG later requiring laser or incisional glaucoma surgery was not significantly different with each additional month of statin exposure, HR 1.002, 95%CI 0.994, 1.010 $P = 0.68$.

C:D, cup disc ratio; n.r., not reported; RR, relative risk.

Table 5. Features and Results of Studies Investigating Association Between Statin Use and IOP

Author	Glaucoma Parameter Definition, IOP	Method Used to Quantify Statin Use	Statin Use Definition	Summary of Statin-Related Primary Outcomes
Leung et al.,[30] 2010	Glaucoma progression IOP: GAT	Systemic use of medications including statins, simvastatin only, noted from computerized database	Statin use positive and statin use negative; continual statin use was checked at each follow-up visit and verified by physician prescription and patient purchase	There were no statistically significant differences between: Median untreated IOP measurement in the group ($n = 31$) that received statins, 15.04 ± 2.47 mm Hg, compared to the group ($n = 225$) who did not, 14.37 ± 2.78 mm Hg $P = 0.213$ Maximum untreated IOP measurements in the group ($n = 31$) that received statins, 17.61 ± 2.93 mm Hg, compared to the group ($n = 225$) who did not, 17.71 ± 3.71 mm Hg $P = 0.865$
Marcus et al.,[25] 2012	Glaucoma incidence IOP: GAT	Automated pharmacy records; provided information on medication name, date of first prescription, and duration of use	No use Cumulative use for less than 2 y Cumulative use for more than 2 y Median length of statin use among statin users was 1424 d	Multiple regression analysis of IOP association with statin use; β −0.006, 95%CI −0.262, 0.249 $P = 0.96$
Khawaja et al.,[31] 2014	Cross-sectional prevalence IOP: ocular response analyzer	Participants brought all current medication and associated documentation to ophthalmic examination where they were recorded on electronic case record form	Cross-sectional prevalence of statin use	1565 of 7093 patients in the study taking statins Mean IOP of participants taking statins versus participants not taking statins, adjusted for possible confounders (age, sex, body mass index, and HbA1c), 15.67 vs. 15.99 mm Hg Difference −0.31, 95%CI −0.51, −0.12 $P = 0.002$ Linear regression model of IOP association with statin use; β −0.29, 95%CI −0.50, −0.09 $P = 0.003$ Following adjustment for nitrate use; β −0.21, 95%CI −0.42, −0.00 $P = 0.045$ Following adjustment for beta-blocker use; β −0.11, 95%CI −0.31, 0.10 $P = 0.31$

GAT, Goldmann Applanation Tonometry; HbA1c, Glycosylated Haemoglobin.

Publication Bias

Funnel plots that plot the OR on the log scale (*x*-axis) against the standard error of the log odds (*y*-axis) were used to examine publication bias and the possibility of type 1 error. In Figure 5 there is no evidence of asymmetry in the funnel plot examining short-term statin use, and consequently no publication bias is apparent in these studies. Funnel plots were not conducted for longer-term statin use and statin use not stratified by length of exposure because too few studies were available.

Sensitivity Analysis

In the sensitivity analysis, the overall heterogeneity and effect size was calculated following exclusion of the studies

Table 6. Newcastle-Ottawa Scale: Cohort Studies

	De et al. 2006	De Castro et al.,[27] 2007	Tong,[28] 2008	Iskedjian et al.[29] 2009	Leung et al.,[30] 2010	Marcus et al.,[25] 2012	Stein et al.,[24] 2012	Khawaja et al.,[31] 2014
Selection								
Representativeness of the exposed cohort	*Somewhat representative of the average OAG patient	*Somewhat representative of the average OAG suspect	No description of the derivation of the cohort	*Somewhat representative of the average patient receiving prescription benefits in Regie de l'assurance malaide du Quebec	*Somewhat representative of the average Chinese patient with normal-tension glaucoma ≥18 y of age	No description of the derivation of the cohort	Selected group of users	*Somewhat representative of the average member of a study population aged between 40 and 79 y living in Norfolk
Selection of the nonexposed cohort	*Drawn from the same community as the exposed cohort	*Drawn from the same community as the exposed cohort	No description of the derivation of the nonexposed cohort	*Drawn from the same community as the exposed cohort	*Drawn from the same community as the exposed cohort	*Drawn from the same community as the exposed cohort	*Drawn from the same community as the exposed cohort	*Drawn from the same community as the exposed cohort
Ascertainment of exposure	No description	*Secure record	No description	*Secure record	*Secure record	*Secure record	*Secure record	*Secure record
Demonstration that outcome of interest was not present at the start of the study	*Yes	*Yes	No	*Yes	*Yes	*Yes	*Yes	*Yes
Comparability								
Comparability of cohorts on the basis of design or analysis; most important factor study controls for		*Age		*Other systemic medication use	*History of disc hemorrhage, history of CVAs, age at baseline, per 10 y older	*Age	*Age	*Age
Study controls for any additional factor		*Sex, race, refractive error, history of diabetes mellitus, coronary artery disease				*NSCLDs, age, sex, IOP, family history of glaucoma, myopia	*NSCLDs, sex, race, education level, household net worth, ocular and medical comorbidities	*Sex, body mass index, HbA1c, beta-blocker, nitrate and aspirin use
Exposure								
Ascertainment of outcome	No description of assessment blinding	No description of assessment blinding	No description	*Record linkage	*Independent blind assessment	*Independent blind assessment	*Record linkage	*Independent blind assessment
Was follow-up long enough for outcomes to occur?	*Yes	*Yes	No	*Yes	*Yes	*Yes	*Yes	*Yes

TABLE 6. Continued

	De et al. 2006	De Castro et al.,[27] 2007	Tong,[28] 2008	Iskedjian et al.[29] 2009	Leung et al.,[30] 2010	Marcus et al.,[25] 2012	Stein et al.,[24] 2012	Khawaja et al.,[31] 2014
Adequacy of follow-up of cohort	*Complete follow-up: all subjects accounted for	*Complete follow-up: all subjects accounted for	No statement	*Complete follow-up: all subjects accounted for	*Subjects lost to follow-up unlikely to introduce bias: 0.4% lost to follow up and description of those lost provided	*Complete follow-up of eligible patients, (3939 of 7983 in cohort): all subjects accounted for	*Complete follow-up of eligible patients: all subjects accounted for	*Complete follow-up of patients who underwent ophthalmic examination, (8623 in cross-sectional study of 25,639 in cohort): all subjects accounted for
Total stars	5, abstract	8	0, abstract	8	8	8	8	9

HbA1c, Glycosylated Haemoglobin.
* A star awarded to the study for that component of the Newcastle Ottawa Scale.

scoring ≤7 in the NOS ($n = 2$). When McGwin et al.[22] was removed from the analysis there was no change in the pooled OR comparing statin use for ≤2 years versus controls (OR 0.96, 95%CI 0.94, 0.99). There was a change in the pooled OR comparing statin use for >2 years versus controls when McGwin et al.[22] was removed but it did not affect the statistical significance of the result (OR 0.71, 95%CI 0.37, 1.38). When McGwin et al.[22] and Chen et al.[26] were removed from the analysis of pooled ORs that were not stratified by length of exposure, there was no effect on the statistical significance of the result (OR 0.77, 95%CI 0.44, 1.35).

Statin Use and Progression of Glaucoma

The association between statin use and progression of glaucoma was reported in four full studies and two abstracts (Table 4). Among these there were five retrospective cohort studies and one prospective cohort study. There were different definitions of glaucoma progression across all of the studies, which meant that meta-analysis could not be performed. There were conflicting results across studies regarding association between statin use and progression. De and coauthors (De M, et al. *IOVS* 2006;47:ARVO E-Abstract 3398) defined progression as the average change in mean deviation of the visual field test per year. They found no statistically significant difference in the average change in mean deviation per year or pattern standard deviation per year between controls and users of statin for greater than 23 months. De Castro et al.[27] defined OAG progression using various clinical parameters. They found no statistical difference among the number of patients who progressed to "outside normal limits" on glaucoma hemifield visual field test in the statin group compared to controls. However, they did find significant differences in the progression of multiple confocal scanning laser ophthalmoscopy parameters per year including rim volume, retinal nerve fiber layer cross-sectional area, and mean global retinal nerve fiber layer thickness, which favored the statins group when adjusted for multiple systemic and ocular factors. An abstract by Tong[28] in 2008 found that univariate analysis of statin use was correlated with stable disease. However, descriptions of the study population, method of assessment, and adjustment for confounders were not reported. The study scored 0 on NOS. Iskedjian et al.[29] used read code data for the addition of adjunctive medical therapy in those taking prostaglandin analogues for glaucoma as a surrogate marker for progression. They found that the proportion of patients initiating adjunctive medical therapy for glaucoma in the statin group was less than in those not taking any systemic medication, although this did not reach statistical significance. In a prospective cohort study of normal-tension glaucoma, Leung et al.[30] found that the proportion of patients who took statins in the group that remained stable was significantly higher than the proportion of patients who took statins in the group who progressed. A logistic regression model adjusting for a history of disc hemorrhages, cerebrovascular disease, and age at baseline showed that simvastatin use conferred a significant protective effect against visual field progression. In a retrospective cohort study, Stein et al.[24] used read code changes from "suspect OAG to OAG diagnosis" and "surgical treatment for OAG" as proxies for progression. Those who took statins for 1 or 2 years had decreased hazard of progressing to OAG from OAG suspect compared to those who did not receive statins (Table 4). However, hazard of an individual with OAG later requiring laser or incisional glaucoma surgery was not significantly reduced with statin exposure.

Table 7. Newcastle-Ottawa Scale: Case–Control Studies

	McGwin et al.,[22] 2004	Owen et al.,[30] 2010	Chen et al.,[26] 2015
Selection			
Is the case definition adequate?	Yes, e.g., record linkage or based on self-reports	Yes, e.g., record linkage or based on self-reports	Yes, e.g., record linkage or based on self-reports
Representativeness of the cases	Potential for selection bias or not stated	*Consecutive or obviously representative series of cases	Potential for selection bias or not stated
Selection of controls	Hospital controls	*Community controls	*Community controls
Definition of controls	*No history of disease, endpoint	*No history of disease, endpoint	*No history of disease, endpoint
Comparability			
Comparability of cases and controls on the basis of design or analysis, most important factor study controls for	*Age	*Year of birth	*Age
Study controls for any additional factor	*Diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, arterial disease	*Practice, sex, ACORN index, selected comorbidities before case diagnosis, number of drugs types prescribed	*Sex, diabetes, year of hyperlipidemia diagnosis, hypertension, depression, Charlson comorbidity index, NSCLD use
Exposure			
Ascertainment of exposure	*Secure record	*Secure record	*Secure record
Same method of ascertainment for cases and controls	*Yes	*Yes	*Yes
Nonresponse rate	*Same rate for both groups	*Same rate for both groups	*Same rate for both groups
Total stars	6	8	7

ACORN, a classification of residential neighborhoods.
* A star awarded to the study for that component of the Newcastle Ottawa Scale.

Statin Use and IOP

The association between statin use and IOP was presented in three studies (Table 5). Leung et al.[30] and Marcus et al.[25] reported no significant changes in IOP associated with statin use. Khawaja et al.[31] reported a significant reduction in IOP among statin users compared to non-statin users when adjusted for age and sex (β –0.31, 95%CI –0.51, –0.12 P = 0.002). However, when adjusted for beta-blocker therapy, the association was no longer significant.

Discussion

To date this is the only systematic review that evaluates the association between statin use and glaucoma. Our search yielded no randomized controlled trials but 11 observational and case–control studies with sample sizes ranging from 76 to over 500,000 participants. Meta-analysis of the effect of short-term statin therapy on the incidence of glaucoma demonstrated a 4% reduced risk of glaucoma; however, long-term therapy did not demonstrate a statistically significant effect. Similarly, we did not find any significant association between statin use and incidence of glaucoma when outcomes were not stratified according to length of exposure to statin therapy. A previous meta-analysis by Macedo et al.[19] evaluating the unintended effects of statins identified only three studies investigating the association with glaucoma and statin use, whereas we have identified a more complete set of evidence. Furthermore those authors did not report on short- versus long-term exposure to statin therapy. Macedo et al.[19] found an overall pooled OR estimate of 0.86 (95%CI 0.69, 1.08).

Read codes are a system by which diagnostic codes are allocated to patients within databases based on the clinical diagnosis as entered in the system, but not necessarily independently validated. The use of read code to classify glaucoma incidence and progression in several studies[22–24,26,29] poses the risk of misclassification bias. Caution must therefore be employed when interpreting these studies. By far the largest identified study was conducted by Stein et al.[24] with a study population of over 500,000 individuals. The sample was identified by the individuals' hyperlipidemia status. Hence the generalizability of these results may be limited to the

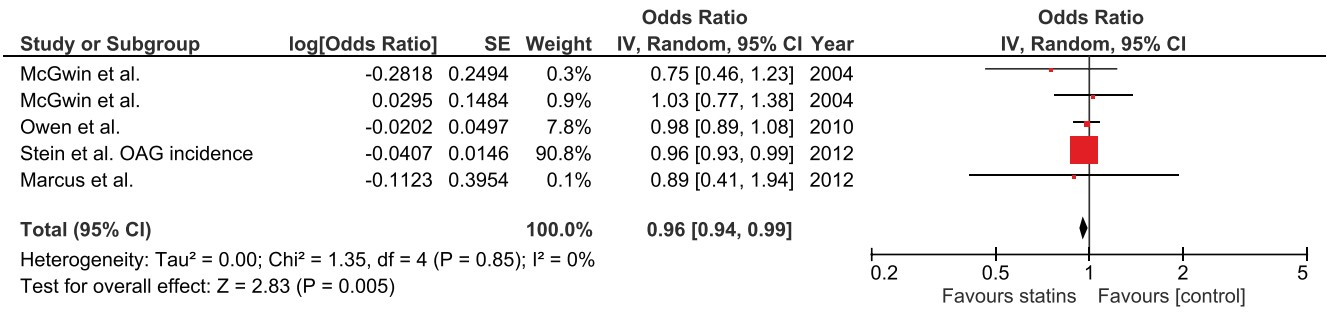


Figure 2. Forest plot of incidence of glaucoma and statin use ≤2 years versus controls. McGwin et al.,[22] refers to exposure for <12 months (*top*) and 12 to 23 months (*second from top*). McGwin et al.,[22] (*second from top*): Upper limit of 95%CI (1.38) is not exactly equivalent to upper limit of 95%CI in Table 3 (1.39) due to rounding in meta-analysis software.

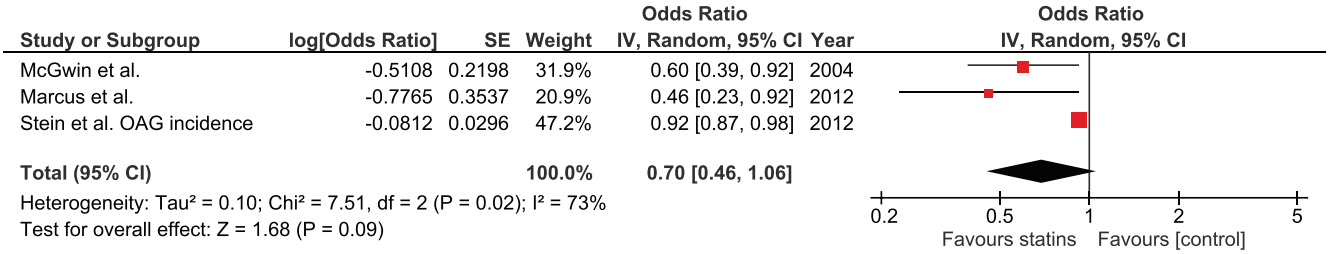


Figure 3. Forest plot of incidence of glaucoma and statin use >2 years versus control. Marcus et al.,[25] upper limit of 95%CI (0.92) is not exactly equivalent to upper limit of 95%CI in Table 3 (0.94) due to rounding in meta-analysis software.

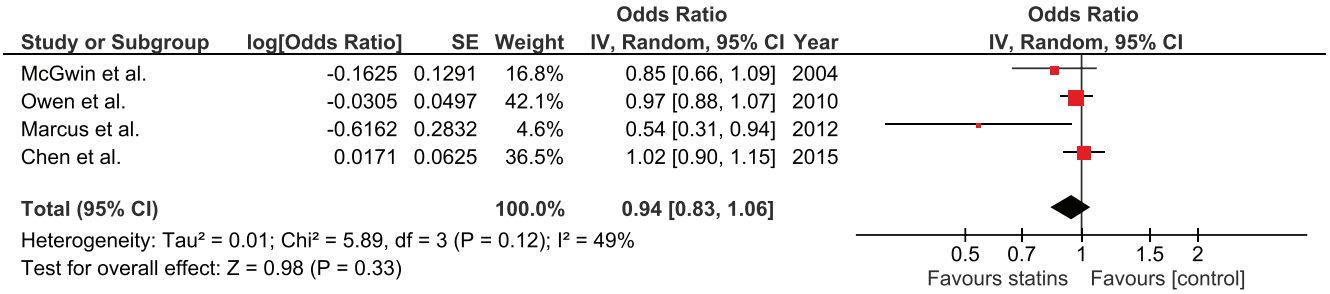


Figure 4. Forest plot of incidence of glaucoma and statin use from outcomes not stratified by length of exposure. Marcus et al.,[25] upper limit of 95%CI (0.94) is not exactly equivalent to upper limit of 95%CI in Table 3 (0.96) due to rounding in meta-analysis software. Owen et al.,[30] upper limit of 95%CI (1.07) is not exactly equivalent to upper limit of 95%CI in Table 3 (1.06) due to rounding in meta-analysis software.

population with hyperlipidemia. As the largest study identified, the study by Stein et al.[24] carries most weight; however, it is retrospective and uses read code data to define glaucoma, and therefore the quality of evidence from this study is relatively poor and the results need to be interpreted with caution.

The use of nonstatin cholesterol-lowering drugs (NSCLDs), a possible confounding factor, was reported by McGwin et al.,[22] Stein et al.,[24] Marcus et al.,[25] and Chen et al.[26] McGwin et al.[22] found that NSCLD use for less than 12 months was associated with reduced incidence of OAG (OR 0.38, 95%CI 0.18, 0.79), and Stein et al.[24] found that persons who took NSCLD for 2 years had a 14% decreased risk of being prescribed a glaucoma medication (adjusted HR 0.862, 95%CI 0.785, 0.946). In contrast, Marcus et al.[25] and Chen et al.[26] did not demonstrate statistically significant protective effects of NSCLDs in glaucoma. In these studies NSCLDs were defined as a heterogeneous group of medications encompassing various classes of drugs. Certain classes of NSCLDs such as peroxisome proliferator–activated receptor alpha (PPARα) agonists (fibrates) have been shown to exhibit immunomodulatory pleiotropic effects independent of their lipid-lowering properties[32] and have been shown to work synergistically with statins.[33–35] Statins may induce IOP lowering by increasing aqueous outflow.[36] The confounding effect of systemic beta-blocker therapy on the effect of statins on IOP lowering was reported by Khawaja et al.[31] They reported that the observed IOP-lowering effect of statins was no longer significant following adjustment for systemic beta-blocker therapy. Thus

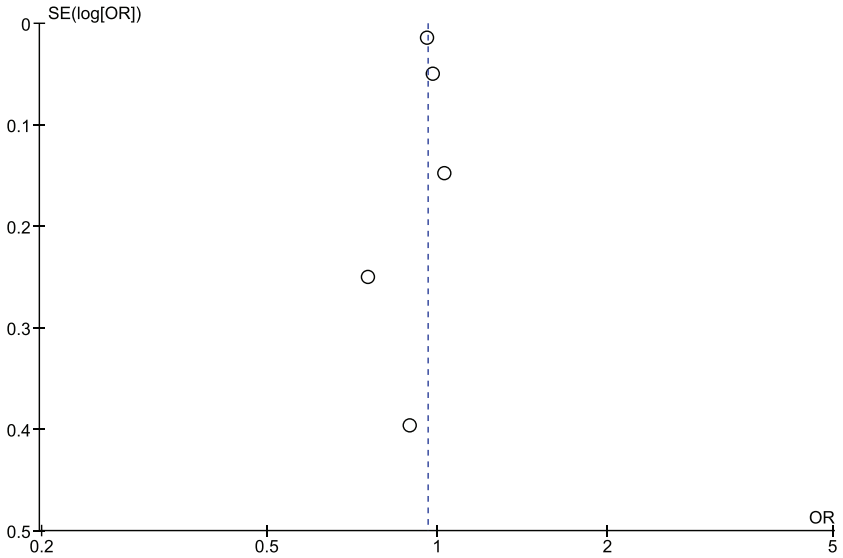


Figure 5. Funnel plot examining publication bias investigating short-term (≤2 years) statin use and incidence of glaucoma.

the confounding effects of NSCLDs and systemic beta-blockers should be considered in the design and analysis of future interventional studies.

From our study we cannot rule out confounding by indication,[37] and we must ask if it is the hyperlipidemia that might be protective or the statin use. A study by Newman-Casey et al.[38] showed that hyperlipidemia was associated with a decreased risk in developing OAG; however, they could not determine whether it was the treatment for hyperlipidemia that reduced the risk or the hyperlipidemia itself. A study by Wang et al.[39] showed that dyslipidemia was not significantly associated with the prevalence of glaucoma; however, they showed that dyslipidemia was associated with higher IOP and beta zone of parapapillary atrophy in a Chinese population. Chen et al.[26] demonstrated that higher dosages of statins are associated with increased risk of OAG (OR 1.24, 95%CI 1.03, 1.49). They proposed that higher dosages of statins were an indication of poorer lipid control that was the cause of the increased risk of OAG.

There were a number of strengths in this review. The sensitivity of our search strategy was maximized by restricting the exclusion criteria during the screening stage. However, the observational studies included are susceptible to various systematic biases depending on whether they are case–control or cohort designs. Case–control studies are generally prone to selection bias and require strict case definition to prevent misclassification bias. Cohort studies are considered methodologically superior to case–control studies; however, they are expensive and must be well conducted to prevent loss to follow-up. Cross-sectional studies are useful to estimate prevalence but are of limited value when investigating incidence. For each study we addressed the risk of bias using a range of tools recommended in *The Cochrane Handbook of Systematic Reviews*.[18] In addition, the comprehensive approach adopted to ascertain confounding factors in each study added to the strength of the review. Potential confounding factors identified and controlled for in each study are outlined in Table 1.

Weaknesses of the study include the exclusion of literature in languages other than English. To reach a wider audience, significant results tend to be published in English; therefore a degree of publication bias may be introduced by language restriction. Our investigation of publication bias did not reveal type 1 error in the results of studies investigating the short-term effects of statin use and incidence of glaucoma. A limitation in our study is that we had too few studies to investigate possible publication bias in studies investigating long-term statin exposure and those not stratified by length of exposure to statins. Although abstracts were identified and included, a formal search of gray literature databases was not performed, which may have contributed to publication bias. Another limitation in the reporting of our results is defining glaucoma as "commencing glaucoma medications" because some people may have ocular hypertension and not glaucoma. However, we addressed this by not including these estimates in the meta-analysis.

In conclusion, the results of our meta-analysis provide evidence for the association between the short-term use of statin therapy and a reduced incidence of glaucoma. However, the observational design of the studies in the meta-analysis limits the ability to make inferences about whether or not exposure to statins causes reduced incidence of glaucoma. There was inconsistent evidence for the IOP-lowering effect of statins and the effect of statins on the progression of OAG. The associations observed in this review warrant a prospective interventional randomized controlled study with short- and long-term follow-up to provide further insight into the role of statin therapy in the prevention of onset or progression of glaucoma and its effects on IOP.

Acknowledgments

Disclosure: **P. McCann**, None; **R.E. Hogg**, None; **R. Fallis**, None; **A. Azuara-Blanco**, None

References

1. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014; 121:2081–2090.
2. Burr JM, Mowatt G, Hernandez R, et al. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11:iii–iv, ix–x, 1–190.
3. Rudnicka AR, Mt-Isa S, Owen CG, et al. Variations in primary open-angle glaucoma prevalence by age, gender, and race: a bayesian meta-analysis. *Invest Ophthalmol Vis Sci*. 2006;47: 4254–4261.
4. Miglior S, Bertuzzi F. Relationship between intraocular pressure and glaucoma onset and progression. *Curr Opin Pharmacol*. 2013;13:32–35.
5. Chang EE, Goldberg JL. Glaucoma 2.0: neuroprotection, neuroregeneration, neuroenhancement. *Ophthalmology*. 2012;119:979–986.
6. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov*. 2004;3:711–715.
7. Bradley D. Why big pharma needs to learn the three 'R's. *Nat Rev Drug Discov*. 2005;4:446.
8. Pritchard JF, Jurima-Romet M, Reimer ML, et al. Making better drugs: decision gates in non-clinical drug development. *Nat Rev Drug Discov*. 2003;2:542–553.
9. van der Most PJ, Dolga AM, Nijholt IM, et al. Statins: mechanisms of neuroprotection. *Prog Neurobiol*. 2009;88: 64–75.
10. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
11. Sillesen H, Amarenco P, Hennerici MG, et al. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial. *Stroke*. 2008;39:3297–3302.
12. Rikitake Y, Liao JK. Rho GTPases, statins, and nitric oxide. *Circ Res*. 2005;97:1232–1235.
13. Vohra R, Tsai JC, Kolko M. The role of inflammation in the pathogenesis of glaucoma. *Surv Ophthalmol*. 2013;58:311–320.
14. Schmeer C, Kretz A, Isenmann S. Therapeutic potential of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors for the treatment of retinal and eye diseases. *CNS Neurol Disord Drug Targets*. 2007;6:282–287.
15. Pokrovskaya O, Wallace D, O' Brien C. The emerging role of statins in glaucoma pathological mechanisms and therapeutics. *Open J Ophthalmol*. 2014;4:124–138.
16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.
17. Panic N, Leoncini E, de Belvis G, et al. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality

of published systematic review and meta-analyses. *PLoS One*. 2013;8:e83138.
18. Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Including non-randomised studies. In: Higgins JPT, Green S, eds. *The Cochrane Handbook of Systematic Reviews of Interventions*. The Cochrane Collaboration; 2008:391–432.
19. Macedo AF, Taylor FC, Casas JP, et al. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. *BMC Med*. 2014;12:51.
20. Vandenbroucke JP, Pearce N. Case-control studies: basic concepts. *Int J Epidemiol*. 2012;41:1480–1489.
21. Magnus M. *Applied Analytic Approaches. Intermediate Epidemiology Methods That Matter*. Burlington, MA: Jones and Bartlett Learning; 2016:176.
22. 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.
23. Owen CG, Carey IM, Shah S, et al. Hypotensive medication, statins, and the risk of glaucoma. *Invest Ophthalmol Vis Sci*. 2010;51:3524–3530.
24. Stein JD, Newman-Casey PA, Talwar N, et al. The relationship between statin use and open-angle glaucoma. *Ophthalmology*. 2012;119:2074–2081.
25. Marcus MW, Muskens RP, Ramdas WD, et al. Cholesterol-lowering drugs and incident open-angle glaucoma: a population-based cohort study. *PLoS One*. 2012;7:e29724.
26. Chen HY, Hsu SY, Chang YC, et al. Association between statin use and open-angle glaucoma in hyperlipidaemia patients: a Taiwanese population-based case-control study. *Medicine*. 2015;94:e2018.
27. 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 Experiment Ophthalmol*. 2007;35:506–513.
28. Tong MK. Correlation of statins and disease progression in patients with normal tension glaucoma. *Clin Experiment Ophthalmol*. 2008;36(supp 1):A264.
29. 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.
30. Leung DY, Li FC, Kwong YY, et al. Simvastatin and disease stabilization in normal tension glaucoma: a cohort study. *Ophthalmology*. 2010;117:471–476.
31. Khawaja AP, Chan MP, Broadway DC, et al. Systemic medication and intraocular pressure in a British population: the EPIC-Norfolk Eye Study. *Ophthalmology*. 2014;121:1501–1507.
32. Chen Y, Hu Y, Lin M, et al. Therapeutic effects of PPARalpha agonists on diabetic retinopathy in type 1 diabetes models. *Diabetes*. 2013;62:261–272.
33. ACCORD Study Group, ACCORD Eye Study Group; Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med*. 2010;363:233–244.
34. Inoue I, Itoh F, Aoyagi S, et al. Fibrate and statin synergistically increase the transcriptional activities of PPARalpha/RXRalpha and decrease the transactivation of NFkappaB. *Biochem Biophys Res Commun*. 2002;290:131–139.
35. Martin G, Duez H, Blanquart C, et al. Statin-induced inhibition of the rho-signaling pathway activates PPARalpha and induces HDL apoA-I. *J Clin Invest*. 2001;107:1423–1432.
36. 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.
37. Salas M, Hofman A, Stricker BHC. Confounding by indication: an example of variation in the use of epidemiologic terminology. *Am J Epidemiol*. 1999;149:981–983.
38. Newman-Casey PA, Talwar N, Nan B, Musch DC, Stein JD. The relationship between components of metabolic syndrome and open-angle glaucoma. *Ophthalmology*. 2011;118:1318–1326.
39. Wang S, Xu L, Jonas JB, Wang YX, You QS, Yang H. Dyslipidemia and eye diseases in the adult Chinese population: the Beijing eye study. *PLoS One*. 2012;7:e26871.

Appendix 1

Table A1. Search Strategies

Search	Results
Medline 24FEB2016	
1. exp hydroxymethylglutaryl-CoA reductase inhibitors/or exp simvastatin/or exp lovastatin/	31,637
2. exp glaucoma, open-angle/or exp glaucoma/or exp low-tension glaucoma/	45,003
3. 1 and 2	15
4. exp intraocular pressure/	31,292
5. 1 and 4	15
6. 3 or 5	23
7. limit 6 to (english language and humans)	23
Embase 24FEB2016	
1. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/	108,897
2. exp glaucoma/or exp low-tension glaucoma/or exp open angle glaucoma/or exp primary glaucoma/	69,034
3. 1 and 2	287
4. exp intraocular pressure/	41,038
5. 1 and 4	68
6. 3 or 5	319
7. limit 6 to (human and english language)	284
PubMed 24FEB2016	
1. "statins AND	
2. "glaucoma"	
Results = 30	
Advanced Google Scholar 24FEB2016	
1. "statins" AND	
2. "glaucoma"	
Results = 6	

Appendix 2

Newcastle-Ottawa Quality Assessment Scales

Case–Control Studies

Note: A study can be awarded a maximum of one star (*) for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

(1) Is the case definition adequate?
  (a) Yes, with independent validation*
  (b) Yes, for example, record linkage or based on self-reports
  (c) No description
(2) Representativeness of the cases
  (a) Consecutive or obviously representative series of cases*
  (b) Potential for selection biases or not stated
(3) Selection of controls
  (a) Community controls*
  (b) Hospital controls
  (c) No description
(4) Definition of controls
  (a) No history of disease (endpoint)*
  (b) No description of source

Comparability

(1) Comparability of cases and controls on the basis of the design or analysis
  (a) Study controls for _____ (select the most important factor)*
  (b) Study controls for any additional factor* (this criterion could be modified to indicate specific control for a second important factor)

Exposure

(1) Ascertainment of exposure
  (a) Secure record (e.g., surgical records)*
  (b) Structured interview where blind to case/control status*
  (c) Interview not blinded to case/control status
  (d) Written self-report or medical record only
  (e) No description
(2) Same method of ascertainment for cases and controls
  (a) Yes*
  (b) No
(3) Nonresponse rate
  (a) Same rate for both groups*
  (b) Nonrespondents described
  (c) Rate different and no designation

Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

(1) Representativeness of the exposed cohort
  (a) Truly representative of the average _____ (describe) in the community*
  (b) Somewhat representative of the average _____ in the community*
  (c) Selected group of users, for example, nurses, volunteers
  (d) No description of the derivation of the cohort
(2) Selection of the nonexposed cohort
  (a) Drawn from the same community as the exposed cohort*
  (b) Drawn from a different source
  (c) No description of the derivation of the nonexposed cohort
(3) Ascertainment of exposure
  (a) Secure record (e.g., surgical records)*
  (b) Structured interview*
  (c) Written self-report
  (d) No description
(4) Demonstration that outcome of interest was not present at start of study
  (a) Yes*
  (b) No

Comparability

(1) Comparability of cohorts on the basis of the design or analysis
  (a) Study controls for _____ (select the most important factor)*
  (b) Study controls for any additional factor* (this criterion could be modified to indicate specific control for a second important factor)

Outcome

(1) Assessment of outcome
  (a) Independent blind assessment*
  (b) Record linkage*
  (c) Self-report
  (d) No description
(2) Was follow-up long enough for outcomes to occur?
  (a) Yes (select an adequate follow-up period for outcome of interest)*
  (b) No
(3) Adequacy of follow-up of cohorts
  (a) Complete follow-up—all subjects accounted for*
  (b) Subjects lost to follow-up unlikely to introduce bias—small number lost: $\leq$20%, or description provided of those lost)*
  (c) Follow-up rate <80% and no description of those lost
  (d) No statement