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

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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 (<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

G
taucoma 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 glaucoma affects 64.3 million people, and this is expected to increase to 111.8 million by 2040.1 The global prevalence of glaucoma affects 64.3 million people, and this is expected to increase to 111.8 million by 2040.1 The global prevalence of glaucoma affects 64.3 million people, and this is expected to increase to 111.8 million by 2040.1 The global prevalence of glaucoma affects 64.3 million people, and this is expected to increase to 111.8 million by 2040.1 The global prevalence of glaucoma affects 64.3 million people, and this is expected to increase to 111.8 million by 2040.1

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 GTPase12 and immunomodulation13 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

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. The global prevalence of glaucoma affects 64.3 million people, and this is expected to increase to 111.8 million by 2040. 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. Major risk factors for OAG include age and intraocular pressure (IOP). Intraocular pressure is currently the only modifiable major risk factor for OAG development and progression. 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. 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. 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. 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. 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. 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. The so-called pleiotropic properties of statins such as inhibition of isoprenylation of Rho GTPase and immunomodulation have been proposed to protect retinal ganglion cells (RGCs) against glaucomatous damage. Thus there has been increasing interest in the potential role of statins in glaucoma pathologic mechanisms and therapeutics. 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
Statins and IOP, Glaucoma Incidence and Progression

METHODS

We followed the MOOSE guidelines\(^\text{16}\) 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\(^\text{17}\) 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. 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. 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 (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 ≤7 as having a lower risk of bias. The cutoff of 7 was used as it had been adopted by a previous review. 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%. The \( \chi^2 \) 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 \( \chi^2 \) distribution with the degrees of freedom equal to the number of studies minus 1. The \( P \) 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 (≤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 ≥8 and the remaining two cohort studies were judged to score ≤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 ≥8 on the NOS, and the other two were judged to have scored ≤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 ≤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., Owen et al., and Stein et al. used diagnostic read codes to define glaucoma incidence, whereas Marcus et al. used a clinical diagnosis. McGwin et al. were...
<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Dataset (Country)</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGwin et al., 2004</td>
<td>Nested case–control study</td>
<td>Veterans Affairs Medical Center (US)</td>
<td>All male patients, 50 y or older, who had at least 1 visit to BVAMC hospital between January 1, 1997 and December 31, 2001</td>
</tr>
<tr>
<td>De et al., 2006, abstract</td>
<td>Retrospective cohort study</td>
<td>University of California, San Francisco (UCSF), and the San Francisco Veterans Affairs Medical Center (US) retrospective chart review</td>
<td>Patients with OAG</td>
</tr>
<tr>
<td>De Castro et al., 2007</td>
<td>Retrospective cohort study</td>
<td>OAG suspects at the Beckman Vision Center (BVC), UCSF (US)</td>
<td>Glaucoma suspects at BVC UCSF from January 2001 to June 2006</td>
</tr>
<tr>
<td>Tong, 2008, abstract</td>
<td>Retrospective cohort study</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Iskedjian et al., 2009</td>
<td>Retrospective cohort study</td>
<td>RAMQ database repository of prescription claims (Canada)</td>
<td>Random sample from 75% of 2.7 million plan recipients</td>
</tr>
<tr>
<td>Leung et al., 2010</td>
<td>Prospective cohort study</td>
<td>Hong Kong Eye Hospital (Hong Kong)</td>
<td>Prospectively recruited cohort of patients from Hong Kong Eye Hospital</td>
</tr>
<tr>
<td>Owen et al., 2010</td>
<td>Nested case–control study</td>
<td>177 practices in DIN-LINK UK primary care database (UK)</td>
<td>Patients in DIN-LINK database of primary care records with minimum of 5-y continuous high-quality records</td>
</tr>
<tr>
<td>Marcus et al., 2012</td>
<td>Prospective cohort study</td>
<td>Rotterdam Study (The Netherlands)</td>
<td>Participants of the Rotterdam Study n = 7983</td>
</tr>
<tr>
<td>Stein et al., 2012</td>
<td>Retrospective cohort study</td>
<td>i3 InVision Data Mart database; beneficiaries in a managed care network throughout the United States (US)</td>
<td>Beneficiaries who received any form of eye care from 2001 to 2009 n = 10,326,832</td>
</tr>
<tr>
<td>Khawaja et al., 2014</td>
<td>Cross-sectional study, within cohort study</td>
<td>EPIC-Norfolk eye study (UK)</td>
<td>EPIC study participants n = 8625</td>
</tr>
<tr>
<td>Chen et al., 2015</td>
<td>Case–control study</td>
<td>National Health Insurance program (Taiwan)</td>
<td>Longitudinal Health Insurance Database (LHID)</td>
</tr>
</tbody>
</table>

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; O/R, 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 malade du Quebec; Sc, 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.
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
OAG incidence, whereas Marcus et al.\textsuperscript{25} used a clinical diagnosis. McGwin et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 1. Extended

<table>
<thead>
<tr>
<th>Author</th>
<th>Confounders Adjusted For</th>
<th>Outcomes Measured</th>
</tr>
</thead>
</table>
| McGwin et al.\textsuperscript{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.\textsuperscript{26} 2006, abstract | n.r. | 1) Mean deviation: mean change per year  
  2) Pattern standard deviation: mean change per year |
| De Castro et al.\textsuperscript{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,\textsuperscript{28} 2008, abstract | 1, 12, 25, all not adjusted for | 1) Association of statins with stable disease: univariate analysis |
| Iskedjian et al.\textsuperscript{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.\textsuperscript{20} 2010 | 1, 7, 9 | 1) Visual field progression with HFA perimetry  
  2) IOP: GAT |
| Owen et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{31} 2014 | 1, 2, 24 | 1) IOP (ORA): mean Goldmann correlated IOP and association with statin use |
| Chen et al.\textsuperscript{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 |
**Table 2. List of Study Design Features**

<table>
<thead>
<tr>
<th>Study</th>
<th>Between 2 or more groups of participants receiving different interventions?</th>
<th>Within the same group of participants over time?</th>
<th>Were participants allocated to groups by:</th>
<th>Time differences?</th>
<th>Location differences?</th>
<th>Treatment decisions?</th>
<th>Participants' preferences?</th>
<th>On the basis of outcome?</th>
<th>Some other process?</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGwin et al., 2004</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>De et al., 2006</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<td>N</td>
<td>Y</td>
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<td>De Castro et al., 2007</td>
<td>Y</td>
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<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>Tong, 2008</td>
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<td>N</td>
<td>N</td>
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<tr>
<td>Leung et al., 2010</td>
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<tr>
<td>Stein et al., 2012</td>
<td>Y</td>
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<tr>
<td>Khawaja et al., 2014</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Chen et al., 2015</td>
<td>Y</td>
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<td>N</td>
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<td>N</td>
<td>Y</td>
<td>N</td>
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</table>

Nonglaucomatous indications for statin therapy (all studies)

Which parts of the study were prospective:
- Identification of participants?
  - Y
- Assessment of baseline and allocation to intervention?
  - Y
- Assessment of outcomes?
  - Y
- Generation of hypothesis?
  - Y

On what variables was comparability between groups assessed:
- Potential confounders?
  - Y
- Baseline assessment of outcome variables?
  - Y

Study design:
- Nested case-control 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>
<thead>
<tr>
<th>Author</th>
<th>Glaucoma Incidence Definition</th>
<th>Method Used to Quantify Statin Use</th>
<th>Statin Use Definition</th>
<th>Summary of Statin-Related Primary Outcomes in Glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGwin et al., 2004</td>
<td>ICD-9-CM diagnostic codes; date first coded taken as diagnosis date, prevalent cases excluded</td>
<td>BVAMC prescription file queried: length of time between initial statin prescription and incidence of glaucoma extracted from the prescription file</td>
<td>&lt;12 mo: 10.2% of cases &lt;12 mo: 7.6% of controls 12–23 mo: 3.2% of cases 12–23 mo: 2.9% of controls &gt;25 mo: 4.5% of cases &gt;23 mo: 4.6% of controls</td>
<td>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</td>
</tr>
<tr>
<td>Owen et al., 2010</td>
<td>DIN-LINK read codes for glaucoma diagnosis and prescriptions for glaucoma and ocular hypertension treatment; date first coded taken as diagnosis date</td>
<td>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</td>
<td>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</td>
<td>Any statin prescription in 5 y before glaucoma diagnosis date; cases, glaucoma 19.6% versus controls 18.7% P &lt; 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 Incidence; 108 of 3959 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 1.41, 95% CI 0.41, 0.97</td>
</tr>
</tbody>
</table>
### Table 3. Continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Glaucoma Incidence Definition</th>
<th>Method Used to Quantify Statin Use</th>
<th>Statin Use Definition</th>
<th>Summary of Statin-Related Primary Outcomes in Glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein et al., 24 2012</td>
<td>ICD-9-CM diagnostic codes; OAG onset, from no previous diagnosis; incidence of medical treatment for OAG</td>
<td>Comprehensive pharmacy records database including number of days for which each participant was prescribed statin</td>
<td>No use</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number of months statin use</td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous statin use for 1 y</td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous statin use for 2 y</td>
<td></td>
<td>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 0.953, 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 0.934, 0.976</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous statin use for 2 y</td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Chen et al., 26 2015</td>
<td>Glaucoma incidence; ICD-9-CM diagnostic codes for OAG diagnosis</td>
<td>Longitudinal Health Insurance Database (Taiwan) drug prescription registry</td>
<td>Duration from initial statin prescription date to index date, diagnosis date: no use; &lt;30 defined daily doses/y; 30–119 defined daily doses/y; &gt;120 defined daily doses/y</td>
<td>Statin use, yes; adjusted glaucoma risk OR 1.02, 95%CI 0.90, 1.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration from initial statin prescription date to index date, diagnosis date: no use; &lt;30 defined daily doses/y; 30–119 defined daily doses/y; &gt;120 defined daily doses/y</td>
<td></td>
<td>&lt;30 defined daily doses/y: adjusted glaucoma risk OR 0.87, 95%CI 0.73, 1.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration from initial statin prescription date to index date, diagnosis date: no use; &lt;30 defined daily doses/y; 30–119 defined daily doses/y; &gt;120 defined daily doses/y</td>
<td></td>
<td>30–119 defined daily doses/y: adjusted glaucoma risk OR 1.03, 95%CI 0.88, 1.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration from initial statin prescription date to index date, diagnosis date: no use; &lt;30 defined daily doses/y; 30–119 defined daily doses/y; &gt;120 defined daily doses/y</td>
<td></td>
<td>≥120 defined daily doses/y: adjusted glaucoma risk OR 1.24, 95%CI 1.05, 1.49</td>
</tr>
</tbody>
</table>

BVAMC, Birmingham Veterans Affairs Medical Center.
<table>
<thead>
<tr>
<th>Author</th>
<th>Glaucoma Progression Definition</th>
<th>Method Used to Quantify Statin Use</th>
<th>Statin Use Definition</th>
<th>Summary of Statin-Related Primary Outcomes in Glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>De et al. 2006</td>
<td>Glaucoma progression; average change in mean deviation and pattern standard deviation per year</td>
<td>Retrospective chart review</td>
<td>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</td>
<td>Average change in mean deviation per year between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Statin users –0.476 dB/y <em>P</em> = 0.3812</td>
<td>Control group, 9 of 39, 23.1% patients progressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Statin plus aspirin users –0.138 dB/y <em>P</em> = 0.3658</td>
<td>Statin-only group, 1 of 12, 8.33% patients progressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspirin only 0.381 dB/y <em>P</em> = 0.7382</td>
<td>Aspirin-only group, 3 of 13, 23.1% patients progressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control 0.2774 dB/y overall <em>P</em> = 0.59</td>
<td>Statin + aspirin group, 2 of 12, 16.7% patients progressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Change per year for pattern standard deviation was also not significantly different between the groups.</td>
<td><em>P</em> = 0.833</td>
</tr>
<tr>
<td>De Castro et al. 2007</td>
<td>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</td>
<td>Documented consistent use of statins and/or aspirin in medical records Each person interviewed over telephone to confirm medication use</td>
<td>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.</td>
<td>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</td>
</tr>
<tr>
<td>Tong. 2008</td>
<td>Glaucoma progression; mean deviation and pattern standard deviation</td>
<td>n.r.</td>
<td>n.r.</td>
<td>Statins associated with stable disease, univariate analysis Cramers V <em>P</em> = 0.099</td>
</tr>
<tr>
<td>Author</td>
<td>Glaucoma Progression Definition</td>
<td>Method Used to Quantify Statin Use</td>
<td>Statin Use Definition</td>
<td>Summary of Statin-Related Primary Outcomes in Glaucoma</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Iskedjian et al., 2009</td>
<td>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</td>
<td>Pharmaceutical records in prescription database read codes identified patients taking systemic medications including statins.</td>
<td>Dispensed statin in at least 2 consecutive or nonconsecutive prostaglandin analogue intervals.</td>
<td>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%; $P &lt; 0.001$ 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%; $P &lt; 0.001$ 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%; $P &lt; 0.001$ compared with those not taking systemic medications, 32.4%.</td>
</tr>
<tr>
<td>Leung et al., 2010</td>
<td>Glaucoma progression or stabilization by perimetry using Anderson criteria in prevalent normal-tension glaucoma cases</td>
<td>Systemic use of medications including statins, simvastatin only noted from computerized database.</td>
<td>Statin use positive and statin use negative; continual statin use checked at each follow-up visit and verified by physician prescription and patient purchase.</td>
<td>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; $P = 0.030$.</td>
</tr>
</tbody>
</table>
Table 4. Continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Glaucoma Progression Definition</th>
<th>Method Used to Quantify Statin Use</th>
<th>Statin Use Definition</th>
<th>Summary of Statin-Related Primary Outcomes in Glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein et al., 24</td>
<td>Glaucoma progression;</td>
<td>Comprehensive pharmacy records</td>
<td>No use</td>
<td>There were 6934 enrollees, 14.0% developed OAG among 49,628 who had been diagnosed as OAG suspect during the lookback 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.</td>
</tr>
<tr>
<td>2012</td>
<td>ICD-9-CM diagnostic codes;</td>
<td>database including number of days for which each participant was prescribed statin</td>
<td>Continuous statin use for 1 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progression, from suspect OAG to OAG</td>
<td>Mean number of days statin coverage: 800 ± 621 (range, 1–3266) d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical treatment for prevalent OAG</td>
<td>96% used medication ≥50 d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C.D, cup disc ratio; n.r., not reported; RR, relative risk.
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>
<thead>
<tr>
<th>Selection</th>
<th>De et al. 2006</th>
<th>De Castro et al., 2007</th>
<th>Tong, 2008</th>
<th>Iskedjian et al., 2009</th>
<th>Leung et al., 2010</th>
<th>Marcus et al., 2012</th>
<th>Stein et al., 2012</th>
<th>Khawaja et al., 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representativeness of the exposed cohort</td>
<td>*Somewhat representative of the average OAG patient</td>
<td>*Somewhat representative of the average OAG suspect</td>
<td>No description of the derivation of the cohort</td>
<td>*Somewhat representative of the average patient receiving prescription benefits in Regie de l’assurance maladie du Quebec</td>
<td>No description of the derivation of the cohort</td>
<td>Selected group of users</td>
<td>*Somewhat representative of the average member of a study population aged between 40 and 79 y living in Norfolk</td>
<td></td>
</tr>
<tr>
<td>Selection of the nonexposed cohort</td>
<td>*Drawn from the same community as the exposed cohort</td>
<td>*Drawn from the same community as the exposed cohort</td>
<td>No description of the derivation of the nonexposed cohort</td>
<td>*Drawn from the same community as the exposed cohort</td>
<td>*Drawn from the same community as the exposed cohort</td>
<td>*Drawn from the same community as the exposed cohort</td>
<td>*Drawn from the same community as the exposed cohort</td>
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</tr>
<tr>
<td>Ascertainment of exposure</td>
<td>No description</td>
<td>*Secure record</td>
<td>No description</td>
<td>*Secure record</td>
<td>*Secure record</td>
<td>*Secure record</td>
<td>*Secure record</td>
<td>*Secure record</td>
</tr>
<tr>
<td>Demonstration that outcome of interest was not present at the start of the study</td>
<td>*Yes</td>
<td>*Yes</td>
<td>No</td>
<td>*Yes</td>
<td>*Yes</td>
<td>*Yes</td>
<td>*Yes</td>
<td>*Yes</td>
</tr>
<tr>
<td>Comparability</td>
<td>*Age</td>
<td>*Other systemic medication use</td>
<td>*History of disc hemorrhage, history of CVAs, age at baseline, per 10 y older</td>
<td>*Age</td>
<td>*Age</td>
<td>*Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study controls for any additional factor</td>
<td>*Sex, race, refractive error, history of diabetes mellitus, coronary artery disease</td>
<td>*NSCLDs, age, sex, IOP, family history of glaucoma, myopia</td>
<td>*NSCLDs, sex, race, education level, household net worth, ocular and medical comorbidities</td>
<td>*Sex, body mass index, HbA1c, beta-blocker, nitrate and aspirin use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascertainment of outcome</td>
<td>*Yes</td>
<td>*Yes</td>
<td>No</td>
<td>*Yes</td>
<td>*Yes</td>
<td>*Yes</td>
<td>*Yes</td>
<td>*Yes</td>
</tr>
<tr>
<td>Was follow-up long enough for outcomes to occur?</td>
<td>*Yes</td>
<td>*Yes</td>
<td>No</td>
<td>*Yes</td>
<td>*Yes</td>
<td>*Yes</td>
<td>*Yes</td>
<td>*Yes</td>
</tr>
</tbody>
</table>
scoring \( \leq 7 \) in the NOS \((n = 2)\). When McGwin et al.\(^2,2\) was removed from the analysis there was no change in the pooled OR comparing statin use for \( \leq 2 \) 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.\(^2,2\) was removed but it did not affect the statistical significance of the result \((OR 0.71, 95\%CI 0.57, 1.38)\). When McGwin et al.\(^2,2\) and Chen et al.\(^2,6\) 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.\(^2,7\) 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\(^2,8\) 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.\(^2,9\) 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.\(^2,0\) 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.\(^2,4\) 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.
The association between statin use and IOP was presented in three studies (Table 5). Leung et al.\textsuperscript{30} and Marcus et al.\textsuperscript{25} reported no significant changes in IOP associated with statin use. Khawaja et al.\textsuperscript{31} reported a significant reduction in IOP among statin users compared to non-statin users when adjusted for age and sex ($\beta = -0.31$, 95%CI $-0.51$ to $-0.12$; $P = 0.002$). 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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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...
population with hyperlipidemia. As the largest study identified, the study by Stein et al.\textsuperscript{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.,\textsuperscript{22} Stein et al.,\textsuperscript{24} Marcus et al.,\textsuperscript{25} and Chen et al.\textsuperscript{26} McGwin et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{25} and Chen et al.\textsuperscript{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 (PPAR\textsubscript{a}) agonists (fibrates) have been shown to exhibit immunomodulatory pleiotropic effects independent of their lipid-lowering properties\textsuperscript{32} and have been shown to work synergistically with statins.\textsuperscript{33–35} Statins may induce IOP lowering by increasing aqueous outflow.\textsuperscript{36} The confounding effect of systemic beta-blocker therapy on the effect of statins on IOP lowering was reported by Khawaja et al.\textsuperscript{31} They reported that the observed IOP-lowering effect of statins was no longer significant following adjustment for systemic beta-blocker therapy. Thus

**Table 1.** Odds ratios of glaucoma incidence and progression associated with statin use.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein et al. OAG incidence</td>
<td>0.92 (0.87, 0.98)</td>
<td>2012</td>
</tr>
<tr>
<td>Marcus et al.</td>
<td>0.46 (0.23, 0.92)</td>
<td>2012</td>
</tr>
<tr>
<td>McGwin et al.</td>
<td>0.60 (0.39, 0.92)</td>
<td>2004</td>
</tr>
</tbody>
</table>

**Figure 3.** Forest plot of incidence of glaucoma and statin use >2 years versus control. Marcus et al.,\textsuperscript{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.,\textsuperscript{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.,\textsuperscript{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.

**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, and we must ask if it is the hyperlipidemia that might be protective or the statin use. A study by Newman-Cassey et al. 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. 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. 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. 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.

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References


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## 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
   - (c) Written self-report or medical record only
   - (d) 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: ≤20%, or description provided of those lost*
   - (c) Follow-up rate <80% and no description of those lost
   - (d) No statement

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