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Author Response: Statin Use and Open-Angle Glaucoma: Evidence From Observational Studies

We read with interest the letter titled “Statin Use and Open-Angle Glaucoma: Evidence From Observational Studies” from Ng and colleagues.1 We would like to thank the authors for the constructive scrutiny of our study design in relation to (1) placement of studies in the meta-analysis, (2) the process of appraising the quality of evidence of the included studies, and (3) appropriateness of inclusion of studies in the systematic review. Below we aim to address the points raised by Ng and colleagues.

1. Placement of studies in the meta-analysis

We thank the authors for raising the discussion regarding our assignment of “suspected glaucoma conversion to open-angle glaucoma (OAG)” as “progression” rather than “incidence.” In light of the definition of OAG suspect in the American Academy of Ophthalmology Preferred Practice Pattern Guidelines,3 we agree that there is room for discussion around this point. We would like to thank the authors for the amended meta-analysis, which includes “suspect to OAG” in the forest plot on incidence of glaucoma and statin use > 2 years. As the authors have noted, development of “outside normal limits” on Humphrey Field Analyzer hemifield measurement should be classified as “incidence of OAG” rather than “progression”; therefore, we have added the results of De Castro et al.4 to the forest plot on incidence of glaucoma and statin use > 2 years.

2. The process of appraising the quality of evidence of the included studies

We thank the authors for raising the discussion regarding our assignment of “suspected glaucoma conversion to open-angle glaucoma (OAG)” as “progression” rather than “incidence.” In light of the definition of OAG suspect in the American Academy of Ophthalmology Preferred Practice Pattern Guidelines,3 we agree that there is room for discussion around this point. We would like to thank the authors for the amended meta-analysis, which includes “suspect to OAG” in the forest plot on incidence of glaucoma and statin use > 2 years. As the authors have noted, development of “outside normal limits” on Humphrey Field Analyzer hemifield measurement should be classified as “incidence of OAG” rather than “progression”; therefore, we have added the results of De Castro et al.4 to the forest plot on incidence of glaucoma and statin use > 2 years.

3. Appropriateness of inclusion of studies in the systematic review

We accept that the case–control study by Owen et al.10 defined cases based on diagnostic codes for glaucoma, prescription for glaucoma medications, and ocular hypertension, and this was described in our study (Table 3 in the article). We agree that there is a lack of information on the proportion of cases with diagnostic code for ocular hypertension. We also accept that ocular hypertension is not a subtype of glaucoma and therefore there is a valid argument for the exclusion of the study from the meta-analyses. However, we believe that discussion of the results in the systematic review and exploration of the implications of removing these results in sensitivity analyses would be pragmatic given the relative lack of studies identified.

We agree that the cross-sectional study by Khawaja et al.12 was not able to infer a causal relationship between statin use and IOP due to its cross-sectional design. However, we disagree that this is justification for the study to be excluded from the systematic review. The identification of concurrent beta-blocker therapy as the explanation for the association between statin therapy and IOP is an important finding.

SENSITIVITY ANALYSIS

A revised sensitivity analysis was conducted following the changes to the NOS scoring and changes to the studies that were included in the forest plots. To address the issue of ocular hypertension in the case mix in the case–control study by Owen et al.,10 sensitivity analysis was performed on meta-analyses that included the results of this study. Removal of Owen et al.10 from the meta-analysis of glaucoma incidence in statin exposure for ≤2 years resulted in no change to the statistical significance of the result (with Owen et al.,10 odds ratio [OR] 0.96, 95% confidence interval [CI] 0.94, 0.98; without Owen et al.,10 OR 0.96, 95% CI 0.93, 0.98). Removal of

<table>
<thead>
<tr>
<th>Study Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGwin et al. (greater than 24m)</td>
<td>-0.5125</td>
<td>0.2189</td>
<td>5.1%</td>
<td>0.60 [0.39, 0.92]</td>
<td></td>
</tr>
<tr>
<td>Stein et al. (no OAG to OAG)</td>
<td>-0.0797</td>
<td>0.0304</td>
<td>47.6%</td>
<td>0.92 [0.87, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Stein et al. (suspect to OAG)</td>
<td>-0.0973</td>
<td>0.0357</td>
<td>44.8%</td>
<td>0.91 [0.85, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Marcus et al.</td>
<td>-0.7765</td>
<td>0.3537</td>
<td>4.2%</td>
<td>0.46 [0.23, 0.92]</td>
<td></td>
</tr>
<tr>
<td>De Castro et al.</td>
<td>-0.7419</td>
<td>0.6995</td>
<td>0.5%</td>
<td>0.48 [0.12, 1.88]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.88 [0.80, 0.97]

Heterogeneity: Tau² = 0.00; Chi² = 8.46, df = 4 (P = 0.08); I² = 53%
Test for overall effect: Z = 2.47 (P = 0.01)

Figure 1. Forest plot of incidence of glaucoma and statin use > 2 years versus control. Marcus et al.7: Upper limit of 95% CI (0.92) is not exactly equivalent to upper limit of 95% CI in Table 3 of original article (0.94) due to rounding in meta-analysis software.
FIGURE 2. Forest plot of incidence of glaucoma and statin use ≤ 2 years versus controls. McGwin et al.9 (12–23 months): Upper limit of 95%CI (1.38) is not exactly equivalent to upper limit of 95%CI in Table 3 of original article (1.39) due to rounding in meta-analysis software.

TABLE 1. Newcastle-Ottawa Scale: Cohort Studies

<table>
<thead>
<tr>
<th>Domain</th>
<th>DeCastro et al.4 2007</th>
<th>Iskedjian et al.5 2009</th>
<th>Leung et al.6 2010</th>
<th>Marcus et al.7 2012</th>
<th>Stein et al.8 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representativeness of the exposed cohort</td>
<td>No description of the derivation of the cohort (university-based eye center) (0)</td>
<td>Somewhat representative of the average patient receiving prescription benefits in Quebec (1)</td>
<td>No description of the derivation of the cohort (0)</td>
<td>Selected group of users (0)</td>
<td></td>
</tr>
<tr>
<td>Selection of the nonexposed cohort</td>
<td>Drawn from the same community as the exposed cohort (1)</td>
<td>Drawn from the same community as the exposed cohort (1)</td>
<td>Drawn from the same community as the exposed cohort (1)</td>
<td>Drawn from the same community as the exposed cohort (1)</td>
<td>Drawn from the same community as the exposed cohort (1)</td>
</tr>
<tr>
<td>Ascertainment of exposure</td>
<td>Medication history collected from medical records and confirmed by phone call (0)</td>
<td>Secure record (1)</td>
<td>Secure record (1)</td>
<td>Secure record (1)</td>
<td>Secure record (1)</td>
</tr>
<tr>
<td>Demonstration that outcome of interest was not present at start of study</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
<td>No/NA (progression as the only outcome) (0)</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
</tr>
<tr>
<td>Comparability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study controls for the most important factor*</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
</tr>
<tr>
<td>Study controls for any additional factor†</td>
<td>DM, CCT, IOP, refractive error (1)</td>
<td>No (0)</td>
<td>DM, CCT, IOP (1)</td>
<td>IOP, myopia (0)</td>
<td>DM (0)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascertainment of outcome</td>
<td>Independent assessment (1)</td>
<td>Record linkage (1)</td>
<td>Independent assessment (1)</td>
<td>Independent assessment (1)</td>
<td>Record linkage (1)</td>
</tr>
<tr>
<td>Was follow-up long enough for outcomes to occur?</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
<td>Yes (1)</td>
</tr>
<tr>
<td>Adequacy of follow-up of cohort</td>
<td>Complete follow-up—all subjects accounted for (1)</td>
<td>Complete follow-up—all subjects accounted for (1)</td>
<td>Subject lost to follow-up unlikely to introduce bias: 0.4% lost to follow-up (1)</td>
<td>Complete follow-up—all subjects accounted for (1)</td>
<td>Complete follow-up—all subjects accounted for (1)</td>
</tr>
<tr>
<td>Total score</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

CCT, central corneal thickness; DM, diabetes mellitus; IOP, intraocular pressure.

* If the study adjusted for age, one mark was scored.
† If the study adjusted for diabetes mellitus and relevant ocular parameters (central corneal thickness, intraocular pressure, or refractive error), one mark was scored.
Selection
Is case definition adequate? Yes, e.g., record linkage or based on self-reports (0)
Representativeness of cases Potential for selection bias or not stated (0)
Selection of controls Hospital controls (0)
Definition of controls No history of disease, endpoint (1)
Comparability Comparability of cases and controls on the basis of design or analysis
Most important factor study controls for Age (1) Year of birth (1) Age (1)
Study controls for any additional factor† Diabetes (0) Diabetes (0) Diabetes (0)
Exposure Ascertainment of exposure Secure record (1) Secure record (1) Secure record (1)
Same method of ascertainment for cases and controls Yes (1) Yes (1) Yes (1)
Nonresponse rate Same rate for both groups (1) Same rate for both groups (1) Same rate for both groups (1)
Total 5 7 6

TABLE 2. Newcastle-Ottawa Scale: Case-Control Studies

CCT, central corneal thickness; DM, diabetes mellitus; IOP, intraocular pressure.
† If the study adjusted for diabetes mellitus and relevant ocular parameters (central corneal thickness, intraocular pressure, or refractive error), one mark was scored.

Owen et al. from the meta-analysis of glaucoma incidence in statin therapy not stratified by length of exposure also resulted in no change to the overall estimate but no change to the statistical significance of the result (without Owen et al., OR 0.88, 95%CI 0.80, 0.97; without Owen et al., OR 0.91, 95%CI 0.84, 0.98). Removal of both McGwin et al. and Owen et al. from the meta-analysis of glaucoma incidence in statin exposure for 2 years resulted in no change to the statistical significance of the result (without both, OR 0.96, 95%CI 0.93, 0.98). Removal of both McGwin et al. and Owen et al. from the meta-analysis of glaucoma incidence in statin exposure for 2 years resulted in no change to the overall estimate and precision (without both, OR 0.79, 95%CI 0.43, 1.45).

Conclusions
Analysis of the data with inclusion of “suspect to OAG” as “incidence” rather than “progression” supports our initial conclusion that short-term statin therapy is associated with reduced incidence of glaucoma. However, the reanalysis following the suggestions by Ng et al. has revealed that long-term statin therapy may be also associated with reduced incidence of glaucoma. As in our initial review we recommend caution when interpreting the results of the meta-analysis because the results of the heavily weighted Stein et al. study are susceptible to misclassification bias and its generalizability is limited to the population with hyperlipidemia. We would again like to thank Ng and colleagues for bringing to our attention some of the limitations of the original analysis and their valuable expertise.

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Augusto Azuara-Blanco

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References

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