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

We read with interest the systematic review and meta-analysis on the effect of statins on intraocular pressure (IOP) and glaucoma incidence and progression by McCann et al.[1] We would like to discuss the appropriateness of inclusion of studies in the systematic review, placement of studies in the meta-analysis, and the process of appraising the quality of evidence of the included studies.

Appropriateness of Inclusion of Studies in the Systematic Review

The authors claim that the systematic review was to evaluate the effect of statins on glaucoma; the inclusion of studies with nonglaucoma cases could lead to erroneous conclusions. The authors included the case–control study by Owen et al.,[2] which defined cases based on a combination of diagnostic codes for glaucoma or ocular hypertension and codes for prescription specific to glaucoma treatment. In the definition of glaucoma, ocular hypertension is not a subtype of glaucoma. There was also a lack of information on the proportion of cases with a diagnostic code of ocular hypertension in the study. With the large uncertainty on the proportion of cases with glaucoma, this case–control study must be excluded from both the systematic review and meta-analysis.

In addition, one of the purposes of the systematic review was to ascertain the effect of statins on IOP. However, the authors did not limit the types of study design for the inclusion of studies. The inclusion of the cross-sectional study by Khawaja et al.[3] in the systematic review was misleading because it does not infer any causal relationship between statin use and IOP. Hence, this cross-sectional study must not be included in the systematic review.

Placement of Studies in the Meta-Analysis

The authors' interpretation of suspected glaucoma as "a form of glaucoma" or "absence of glaucoma" is critical. It determines whether studies regarding the conversion from suspected glaucoma to definite glaucoma[4,5] should be assigned to the outcome of glaucoma incidence or glaucoma progression in the meta-analysis. This in turn alters the conclusion of the meta-analysis.

The authors categorized the patients in the study by Stein et al.[5] who had conversion from suspected glaucoma to definite glaucoma, as well as the patients in the study by De Castro et al.[4] who had within-normal-limits result on the glaucoma hemifield test at the start of study (i.e., open-angle glaucoma [OAG] suspect as defined in the study) but outside normal limits at the last visit (i.e., OAG case as defined in the study) as having glaucoma progression. They also categorized the patients with normal-tension glaucoma in the study by Leung et al.[6] who had visual field defect at the start of the study and visual field progression at the end of the study as having glaucoma progression. In fact, these two groups of patients were of different clinical diagnoses. The American Academy of Ophthalmology Preferred Practice Pattern Guidelines[7] defines primary OAG suspect as "an individual with clinical findings and/or a constellation of risk factors that indicate an increased likelihood of developing primary OAG" (p. 210). This implies the nonnecessity for suspected glaucoma to "progress" to definite glaucoma with time. Therefore, it is disputable whether suspected glaucoma should be referred to as an early stage of glaucoma and assigned to the outcome of glaucoma progression in the meta-analysis.

It is noteworthy that the conclusion of the meta-analysis in Figure 3 of the article will be different if suspected glaucoma is considered as "absence of glaucoma." The outcome of conversion from glaucoma suspect to glaucoma in the study by Stein et al.[5] has then to be placed under the outcome of glaucoma incidence rather than glaucoma progression. The insignificant protective effect (pooled odds ratio, 0.70; 95% confidence interval, 0.46 to 1.06) of long-term use (>2 years) of statin on development of glaucoma will become significant (pooled odds ratio, 0.88; 95% confidence interval, 0.80 to 0.98) (see Figure).[5,8,9] Therefore, elucidating the interpretation of suspected glaucoma for assigning studies to different outcomes is of paramount importance.

The Process of Appraising the Quality of Evidence of the Included Studies

The Newcastle-Ottawa Scale (NOS)[10] was used for assessing the quality of observational studies in the systematic review. We are doubtful of the consistently high quality score of the included cohort studies with full text available in the systematic review, with all of them receiving an NOS score of 8 or above (out of 9) (Table 6 of the article).

First, the authors stated that the studies by De Castro et al.[4] and Leung et al.[6] consisted of representative or somewhat representative samples of statin users in the selection domain. However, the representativeness of both studies is uncertain because they were conducted in university-based eye centers where the population coverage was not described.

Second, the authors considered that all cohort studies had secure records on exposure of statin in the selection domain. However, De Castro et al.[4] stated that the data on statin and aspirin exposure were collected from medication history of medical records and confirmed by phone call. Our point of view is to consider only prescription records from a pharmacy or computerized network as "secure records" of exposure, as well demonstrated in the remaining included cohort studies.[5,6,9,11]

Third, the authors claim that the studies by De Castro et al.[4] and Leung et al.[6] demonstrated the absence of outcome of interest at the start of the study. In fact, both studies involved progression as an outcome, with the former being changes in optic nerve head parameters as the main outcome and the latter visual field progression as the only outcome. According to NOS, a cohort study can be scored in the selection domain when there is a demonstration that the outcome of interest was not present at the start of study. However, it seems to be applicable only to incidence rather than progression studies; no clear criteria were set for progression studies. For progression studies, either a comparable or statistical adjustment for baseline progression rate between the exposed and nonexposed cohort is required for drawing an unbiased conclusion. However, we notice that the studies by Castro et al.[4] and Leung et al.[6] did not state the baseline rate of progression of the exposed and nonexposed groups. This piece of information is important, as the rate of progression of glaucoma depends on its baseline severity.[12,13] We suggest that the authors might provide further information on their rationale for scoring these

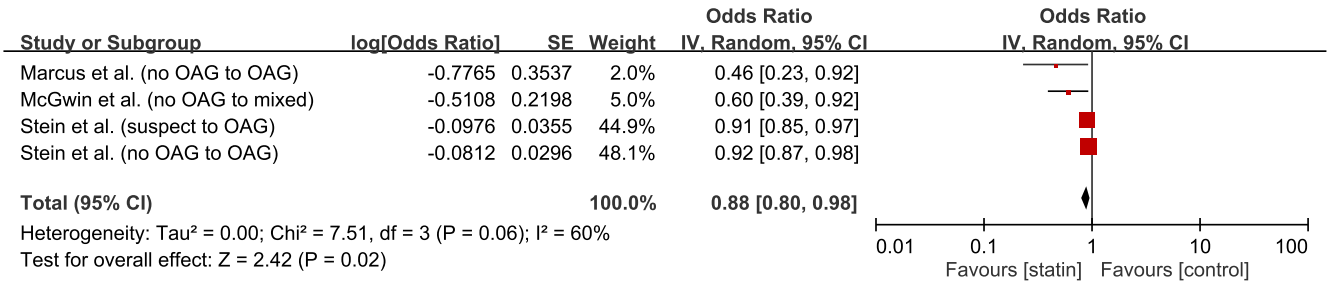

Figure. A reproduction of the authors' Figure 3 forest plot on incidence of glaucoma and statin use > 2 years versus control. The case–control study by McGwin et al.[8] consisted of 25% cases of open-angle glaucoma (OAG) and 75% cases of unspecified or other specified form of glaucoma. The outcome of the remaining two cohort studies by Marcus et al.[9] and Stein et al.[5] was incidence of OAG.

Table. A Reproduction of the Authors' Table 6 of Newcastle-Ottawa Scale: Cohort Studies. Only Cohort Studies With Full Text Available Are Included. The Study by Khawaja et al.[3] Was Removed as It Is Not a Cohort Study

Domain	De Castro et al.[4]	Iskedjian et al.[11]	Leung et al.[6]	Marcus et al.[9]	Stein et al.[5]
Selection					
Representativeness of the exposed cohort	No description of the derivation of the cohort (university-based eye center) (0)	Somewhat representative of the average patient receiving prescription benefits in Regie de l'assurance maladie du Quebec (1)	No description of the derivation of the cohort (university-based eye center) (0)	No description of the derivation of the cohort (0)	Selected group of users (0)
Selection of the nonexposed cohort	Drawn from the same community as the exposed cohort (1)	Drawn from the same community as the exposed cohort (1)	Drawn from the same community as the exposed cohort (1)	Drawn from the same community as the exposed cohort (1)	Drawn from the same community as the exposed cohort (1)
Ascertainment of exposure	Medication history collected from history taking and confirmed by phone call (0)	Secure record (1)	Secure record (1)	Secure record (1)	Secure record (1)
Demonstration that outcome of interest was not present at start of study	No (progression as the main outcome) (0)	Yes (1)	No (progression as the only outcome) (0)	Yes (1)	Yes (1)
Comparability					
Study controls for the most important factor*	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
Study controls for any additional factor†	DM, CCT, IOP, refractive error (1)	No (0)	DM, CCT, IOP (1)	IOP, myopia (0)	DM (0)
Outcome					
Ascertainment of outcome	Independent assessment (1)	Record linkage (1)	Independent assessment (1)	Independent assessment (1)	Record linkage (1)
Was follow-up long enough for outcomes to occur?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
Adequacy of follow-up of cohort	Complete follow-up—all subjects accounted for (1)	Complete follow-up—all subjects accounted for (1)	Subject lost to follow-up unlikely to introduce bias: 0.4% lost to follow-up (1)	Complete follow-up—all subjects accounted for (1)	Complete follow-up—all subjects accounted for (1)
Total score	6	8	7	7	7

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.

two progression studies or indicate the criterion as "not applicable."

Fourth, the authors did not specify and explain the criteria of scoring for the consideration of other important factors in controlling confounding factors in the comparability domain. The comparability domain in NOS involves adjustment for age and other additional factors to control confounding, in which the additional factors can be modified according to the review question of interest.[10,14] As well demonstrated in the study by Zhong et al.,[15] we would like to emphasize that a systematic review should predefine and state explicitly what factors are regarded as "important" in order to enable reproducibility of the NOS score. Since diabetes mellitus[16,17] and ocular parameters such as higher IOP,[16] thinner central corneal thickness,[16] and myopia[16] are important risk factors associated with OAG, both diabetes mellitus and relevant ocular parameters should be controlled to get one mark scored. In the systematic review, Iskedjian et al.[11] adjusted for age but not for any systemic condition and ocular parameter, while their study was scored for adjustment for other systemic medication use. Stein et al.[5] did not adjust for any relevant ocular parameters, but their study was scored for adjustment for other important factors. De Castro et al.[4] and Leung et al.[6] did cover both systemic and ocular elements, but only the study by De Castro et al.[4] was scored for adjustment for other important factors. We postulate that the inconsistency arose as a result of methodological difference in statistical analysis between the two studies, with De Castro et al.[4] adjusting for all factors in the regression model while Leung et al.[6] did not include the insignificant factors at initial univariate analysis in the final regression model.

Finally, the authors did not appreciate the independent assessment of outcome in the study by De Castro et al.,[4] where an automated visual field analyzer was used, similarly to the study by Leung et al.[6] and Marcus et al.[9]; only the latter two studies were scored in the outcome domain. In short, the NOS score for some cohort studies should be revised (see Table)[4–6,9,11] and a sensitivity analysis to exclude studies with poorer methodological quality ($\leq$7) should be performed again.

In conclusion, we respectfully disagree with inclusion of the case–control studies by Owen et al.[2] in both the systematic review and meta-analysis and the cross-sectional study by Khawaja et al.[3] in the systematic review. In carrying out the meta-analysis, there is still room for discussion on the assignment of suspected glaucoma to incidence or progression outcome. Care should be taken in performing quality assessment for observational studies to obtain a reproducible NOS score. We congratulate the authors on their great work on the first systematic review and meta-analysis to summarize the effect of statins on OAG and look forward to their reply.

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