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The Role of Statins and Cholesterol in the Primary Prevention of Primary Open-Angle Glaucoma

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Primary prevention remains the ultimate challenge and noblest goal for averting the debilitating consequences of chronic disease. In glaucoma, lowering of intraocular pressure remains the only known modifiable risk factor to prevent disease development. The identification of new avenues for intervention, prior to the establishment of disease, is of utmost importance given the anticipated rise in glaucoma prevalence worldwide, especially among high-risk populations.¹

In this issue of *JAMA Ophthalmology*, Kang et al² identified a positive association between hypercholesterolemia and incident primary open-angle glaucoma (POAG), and an inverse association between long-term statin use (≥ 5 years) and incident POAG from pooling 3 large, longitudinal cohort studies comprising a total of 136 782 participants who together contributed more than 15 person-years to the analysis. Although the measured effects were modest, the study contributes valuable evidence to the association between cholesterol, statin use, and the risk of POAG, which appears to be consistent with findings across studies in many different populations. Marcus and colleagues³ previously explored this hypothesis in the Rotterdam Study. They reported that long-term use of statins appeared to be associated with a reduced risk of open-angle glaucoma. The observed association was independent of intraocular pressure. A similar finding was reported in persons with hyperlipidemia enrolled in a national US managed care network between 2001 and 2009.⁴ However, there have been conflicting results regarding the association between statins and POAG, with at least 1 study demonstrating an increased risk of glaucoma with statin use.⁵

The strengths of the study by Kang et al² include the sample size, frequency, and length of follow-up among the cohorts. The data were collected biennially in the Nurses' Health Study (2000–2014), Nurses' Health Study 2 (1999–2015), and Health Professionals Follow-up Study (2000–2014). In addition, the case definitions for incident POAG were well-defined, requiring not only medical record confirmation of self-reported glaucoma, but also a detailed review of slitlamp biomicroscopy results and visual field testing to verify the correct diagnosis of POAG and exclude other forms of glaucoma. To have used these comprehensive criteria to identify 886 incident cases of POAG is laudable. Although medication use and

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cholesterol levels were self-reported, the health care personnel who were the participants in these studies may have had higher than usual accuracy in their reporting.

On the other hand, the characteristics of the participants were also a limitation of this study. These are not population-based cohorts, each being composed of health care personnel who may (or more likely may not) be representative of persons in the United States at the highest risk of POAG and whose risk factor profile may differ. The authors note that participants included few African American individuals (0.3%–1.6% among all subgroups reported), one of the groups in the United States at highest risk for POAG.⁶ Also, health care personnel may differ from the general population with regard to many behavioral determinants of health (eg, smoking, alcohol consumption, nutrition, exercise, and occupational exposures). Relative homogeneity of behaviors within and among the 3 cohorts could impair the identification of associations that required larger exposure variability in confounders. Also, persons who receive evaluation and therapy for elevated cholesterol may visit eye care professionals more frequently than those who do not receive such care. Additional exposures that could affect the findings of this study include the possible exposure to other medications that are taken more frequently by statin users (eg, β -blocker use may be protective). Finally, the authors noted appropriately that this study examined a large number of variables, which may have led to overanalyzing the data in search of associations, some of which could be chance findings.

The hypothesized biological bases for the identified association of statin use with a reduced incidence of POAG are wide ranging, which, as Kang et al² noted, could include increased nitric oxide production and improved aqueous outflow facility in the trabecular meshwork, increased blood flow to the optic nerve, and neuroprotective effects on the retinal ganglion cells. Genes involved in cholesterol metabolism have also been implicated with POAG in genome-wide association studies.⁷

Based on the current evidence, it is somewhat premature to advise patients at risk for development of glaucoma to initiate statins solely for the primary prevention of POAG and no conclusions can be drawn regarding what outcome, if any, statins may have on patients who already have a diagnosis of POAG. Further investigation into the biological basis for the association between statins and POAG is needed, and if confirmed, future studies would need to ascertain the optimal dosage and timing of statin initiation for glaucoma prevention.

Much of current glaucoma research focuses on tertiary prevention with the goal of limiting disability in patients with established glaucoma through the development of new medications and surgical devices. This study highlights the importance of continued investigation into opportunities for the primary prevention of POAG, which will require further elucidation of underlying biological mechanisms and testing of promising interventions in high-risk populations.

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