

COMPREHENSIVE

Statins and the Eye: Making Sense of the Data

BY MIRIAM KARMEL, CONTRIBUTING WRITER

INTERVIEWING JAMES C. BOBROW, MD, DONALD S. FONG, MD, MPH, MARK PACKER, MD,
AND JOSHUA D. STEIN, MD, MS

Statins, the blockbuster class of drugs prescribed to prevent coronary artery disease, may have a protective effect in the eye. Or they may not, depending on the studies you read.

Two new additions to the literature exemplify the conflicting nature of statin research. One, a glaucoma study, found an effect so compelling that it may lead to a randomized clinical trial.¹ The other study, on statins and cataract surgery, found a protective effect in one subset of patients but not in another,² suggesting that any effect may just be statistical noise.

“The problem is what to make of this information because it’s not unequivocal,” said James C. Bobrow, MD, speaking of the literature on statins and the eye. Dr. Bobrow is professor of clinical ophthalmology and visual sciences at Washington University School of Medicine in St. Louis. And though he calls statins “potent pharmacological agents, extremely effective in places where they work,” he questions whether their benefits in the eye are due to cause and effect or correlation.

In other words, said Dr. Bobrow, the changes observed in some studies may be brought about by some common mechanism that we’re *not* measuring. Consider, for example, three beverages that can make you inebriated: scotch and soda, rye and soda, gin and soda. Soda is common to each drink, yet we know it isn’t the intoxicating agent. Are statins like soda? Or do they have a true effect on the eye?

Cataract and Statins

Donald S. Fong, MD, MPH, lead author of the cataract study, is a retina specialist, epidemiologist, and director of clinical trials at Kaiser Permanente Southern California, in Baldwin Park. He has an interest in the ocular safety of systemic medications. “Very few monitoring studies have looked at the effect of these drugs on the eye,” he said. He decided to focus on cataract surgery because it is the most common eye surgery and on statins because of their widespread use. (One in four adults aged 45 and older take statins.³ Atorvastatin [Lipitor] was the leading prescription drug sold in the world in 2002.⁴)

Findings from the Kaiser database.

Dr. Fong’s team conducted a case-control study using the Kaiser Permanente database. The study subjects were aged 50 years or older and had been enrolled in Kaiser for at least five years.² The authors defined cases as patients who had first-eye cataract surgery in 2009 (13,982 patients) and controls as those who had an eye exam, but no diagnosis of or surgery for cataract, in 2009 (34,049 patients).

The researchers then looked at the prevalence of statin use among cases and controls. “I thought it would be amazing if the use of statins would lead to fewer cataract extractions,” Dr. Fong said. “The easy hypothesis was that patients with cataract surgery were less likely to use statins. But we didn’t find that.” Instead, they found that, overall, the proportion of statin

Statins and Cataract



Does the use of statins speed or retard the progression of cataracts? Evidence is mixed and may depend on the patient’s age.

users was higher in the cataract surgery group (64.3 percent) than in the control group (55.5 percent).²

He said the findings made sense, given that people who have cataract surgery are older, and statin use increases with age. So his team drilled down and conducted an age-stratified regression analysis. “That’s where we found a difference,” Dr. Fong said. “I found an effect that is modulated by age and how long you take the drug,” he continued. “If you’re older [65+ years], statin use is probably not going to help you because the cataract has already developed.” Once the lens is damaged you can’t fix it, he explained, because the epithelium (which provides the metabolism for the entire lens) is only on the surface. There is

no cellular activity below the surface to repair the damage. However, in the younger group (50 to 64 years), it was protective—probably because cataracts had not yet formed—but only after five or more years of use. Shorter-term statin use (less than five years) was associated with an increased risk of surgery in both age groups.

Are statins antioxidants? Dr. Fong is trying to understand the cause of the protective effects he found. One possible explanation is that a reduction of serum cholesterol might prevent accumulation of lipoproteinaceous deposits in the lens epithelium. Statins might also inhibit lens epithelial cell death. This supports the theory that oxidative damage to the lens epithelium may cause proteins to coagulate and form cataracts. Perhaps statins scavenge the free radicals that damage the lens with light and oxygen.

Dr. Bobrow isn't convinced. "The literature on statins does not include a mechanism for reduction in oxygen saturation or suppression of free radicals in the eye. In fact, no one has measured the concentration of statins in ocular tissue," he said.

On the other hand, Mark Packer, MD, clinical associate professor of ophthalmology at Oregon Health & Science University in Eugene, said that statins as antioxidants could have a biochemical basis, since the denaturing of lens proteins tends to occur because of sunlight and oxygen.

Contradictory results. In the meantime, a recent chart review study of 6,397 patient files at the University of Waterloo, Ontario, found that patients taking statins for type 2 diabetes had an increased risk of developing nuclear sclerosis and cortical cataract.⁵ Yet Dr. Fong noted that both the Beaver Dam and Blue Mountains eye studies found that statin use reduced the risk of cataract development.

Glaucoma and Statins

Joshua D. Stein, MD, MS, and colleagues coauthored a 2011 study on metabolic syndrome and glaucoma, which found that patients with one disorder in the syndrome—hyperlipid-

What About Other Eye Diseases?

Statins reduce serum cholesterol by inhibiting the enzyme hydroxymethylglutaryl-CoA reductase and have been shown to reduce coronary artery disease. "Statins work on a set of enzymes that are present in many tissues in the body," Dr. Bobrow said. "And they do make significant changes in endogenous cholesterol production."

Given statins' possible effect on tissues throughout the body, it isn't surprising that they have been studied for harmful or beneficial associations with a wide range of eye disorders apart from cataract and glaucoma. Results have been mixed.

For example, statin use has been associated with reversible myopathy manifested as diplopia, blepharoptosis, or ophthalmoplegia.¹ On the other hand, the Blue Mountains Eye Study found that statins had a beneficial effect in reducing the risk of indistinct soft drusen, a precursor to age-related macular degeneration.² More recently, statins were shown to affect retinal microcirculation by causing significant vasodilation in retinal venules and arterioles.³

A major limitation of these studies—and indeed, all studies to date on statins and the eye—is that none have been randomized controlled trials. Therefore, although some of these findings eventually may have clinical applicability, for now they serve to point out future research directions.

1 Fraunfelder FW et al. *Ophthalmology*. 2008;115(12):2282-2285.

2 Tan JS et al. *Am J Ophthalmol*. 2007;143(4):685-687.

3 Terai N et al. *Acta Ophthalmol*. 2011;89(6):e500-e504.

emia—had a 5 percent reduction in the risk of open-angle glaucoma (OAG).⁶ What was responsible for that effect: hyperlipidemia itself or the statin medications used to treat it? Was there a relationship between statin use and reduction in the development of OAG, progression from glaucoma suspect to OAG diagnosis, or the need for medical or surgical intervention?

To answer these questions, Dr. Stein, who is assistant professor of ophthalmology and visual sciences at the University of Michigan Kellogg Eye Center, conducted a longitudinal analysis of 524,109 patients over 60 years old with hyperlipidemia.¹ More than 60 percent were taking one or more statin drugs, 4 percent were on nonstatin cholesterol-lowering medications, and more than a third were not using any cholesterol-lowering drugs.

He and his team found that statin use was associated with a reduced risk of developing OAG. After one year, the risk of developing OAG among statin users declined 4 percent compared with those not taking the drugs. At two years, the risk fell 8 percent. What's more, 14 percent of glaucoma suspects converted to an OAG diagnosis, but those who took statins for one

year had a 5 percent decreased hazard of progression to OAG, and those who took them for two years had a 9 percent reduced risk of progression.¹

Dose response found. The glaucoma study, like Dr. Fong's on cataracts,² found that statins worked better over time. But unlike the cataract study, patient age didn't matter. "Regardless of age, those who consumed statins had a protective effect," Dr. Stein said.

However, he said, duration of treatment was a factor: People who took statins for more than two years had a greater benefit than those who took them for one year. There was a dose-response effect. He added that other studies also have shown that extended use of statins is associated with a reduced risk compared with shorter periods of consumption.^{7,8}

Possible mechanisms for statin effects. Nonstatin cholesterol-lowering drugs did not yield an effect in Dr. Stein's study. Dr. Fong had a similar finding, suggesting there may be something inherently beneficial in statins.

Dr. Stein noted three possible mechanisms for statins' effects on the eye.

- Statins regulate nitric oxide synthase (NOS), which causes vasodilation and increased retinal and

choroidal blood flow. Better blood flow to the optic nerve and nerve fiber layer might enhance perfusion to those structures, which might protect against glaucomatous damage.

- Some studies show a neuroprotective effect in rats, perhaps by protecting against apoptosis in the central nervous system. A team from the Netherlands recently reported that statins may be associated with a reduced risk of OAG, yet the prospective population-based cohort study (3,939 participants) found no effect on IOP.⁷ These findings, said Dr. Stein, are consistent with a growing body of literature showing that statins may be useful for diseases of the central nervous system, including stroke, multiple sclerosis, and even Alzheimer disease. “Since the structures that are affected by glaucoma—the optic nerve and retinal nerve fiber layer—are extensions of the central nervous system, we hypothesized that statins might reduce the risk of OAG,” he said.

- Statins may lower IOP by affecting some enzymes that work at the trabecular meshwork, in turn improving outflow of aqueous humor.

Implications for Practice

Although the cataract study suggests that statin use appears to be safe and that longer-term statin use might be helpful in younger patients, Dr. Fong said it is premature to recommend statins for prevention of cataract. “Ophthalmologists don’t need to do anything right now.”

Dr. Packer noted that when he worked on the Academy’s *Preferred Practice Pattern* guidelines for cataract a few years ago, the panel acknowledged that some studies found a protective effect. “It was good news,” he said. “But it was only suggestive. So far, certainly, nothing has been proven.”

In regard to OAG, Dr. Stein agreed. “Although there’s mounting evidence that statins may be beneficial, it’s premature to change practice patterns,” he said. “We’re very excited about our findings that statins appear to reduce the risk of OAG progression in early glaucoma and in suspects. But to take

someone who doesn’t have high cholesterol and start them on statins, we need a randomized controlled trial.”

In fact, if Dr. Stein gets the go-ahead from the National Eye Institute (NEI), he and his colleagues plan to conduct a randomized controlled clinical trial to study progression in patients with early glaucoma who are not on statins. One group will receive prostaglandin analogues, and the other will get prostaglandins plus statins.

If statins prove protective, glaucoma specialists may have a new approach for prevention or even treatment. “We really don’t have options, other than lowering IOP further,” Dr. Stein said. “So if we can identify other agents that protect from damage, that would help us greatly.”

In the meantime, said Dr. Fong, “We as ophthalmologists should remember that drugs that are given systemically might have effects on the eye. We need more studies in this area.”

1 Stein JD et al. *Ophthalmology*. 2012; 119(10):2074-2081.

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5 Machan CM et al. *Optom Vis Sci*. 2012; 89(8):1165-1171.

6 Newman-Casey PA et al. *Ophthalmology*. 2011;118(7):1318-1326.

7 Marcus MW et al. *PLoS One*. 2012; 7(1):e29724.

8 McGwin G Jr et al. *Arch Ophthalmol*. 2004; 122(6):822-826.

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Dr. Fong receives grant support from Allergan and is a consultant for ThromboGenics.

Dr. Packer is a consultant for Abbott Medical Optics, Advanced Vision Science, Allergan, Bausch + Lomb, Corinthian, General Electric, Ista, LensAR, mTuitive, NewSee, Rayner Intraocular Lenses, Surgiview, Transcend Medical, TrueVision, and WaveTec. Dr. Stein has applied for an NEI grant to develop a clinical trial to study statin use in OAG.

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