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Clinical Research

Statin Use and Risk for Cataract: A Nested Case-Control Study of 2 Populations in Canada and the United States

Stephanie J. Wise, MD,[a] Nawaaz A. Nathoo, MD,[a] Mahyar Etminan, PharmD, MSc,[b] Frederick S. Mikelberg, MD, FRCSC,[a] and G.B. John Mancini, MD, FRCPC, FACP, FACC[c]

[a] *Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada*

[b] *Child and Family Research Institute, University of British Columbia, Vancouver, British Columbia, Canada*

[c] *Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada*

See editorial by Gryn et al., pages 1508-1510 in this issue.

ABSTRACT

Background: In current literature the association between statin use and cataracts is inconsistent and controversial. We sought to further examine the effect of statin use on the risk of cataract and need for surgical intervention in 2 North American populations.

Methods: This retrospective nested case-control study derived data from the British Columbia (BC) Ministry of Health databases from 2000-2007 and the IMS LifeLink database from 2001-2011 to form 2 patient cohorts. The BC cohort was comprised of female and male patients; 162,501 patients were matched with 650,004 control subjects. The IMS LifeLink cohort was comprised of male patients aged 40-85 years; 45,065 patients were matched with 450,650 control subjects. Patients with statin use for > 1 year before the initial ophthalmology visit were identified. Diagnosis and surgical management of cataract were followed. Conditional logistic regression models were used to analyze data.

RÉSUMÉ

Introduction : Dans la littérature actuelle, le lien entre l'utilisation des statines et les cataractes est contradictoire et controversé. Nous avons cherché à examiner davantage l'effet de l'utilisation des statines sur le risque de cataractes et la nécessité de l'intervention chirurgicale dans 2 populations nord-américaines.

Méthodes : Les données de cette étude de type cas-témoins imbriquée dans une cohorte rétrospective provenaient des bases de données du ministère de la Santé de la Colombie-Britannique (C.-B.) de 2000 à 2007 et de la base de données du IMS LifeLink de 2001 à 2011 pour former 2 cohortes de patients. La cohorte de la C.-B. comprenait des patients de sexe féminin et de sexe masculin; 162 501 patients ont été appariés à 650 004 témoins. La cohorte de la IMS LifeLink comprenait des hommes de 40 à 85 ans; 45 065 patients ont été appariés à 450 650 témoins. Nous avons déterminé les patients qui utilisaient les statines depuis > 1 an avant la visite initiale

Cataracts are the leading cause of blindness worldwide.[1] It has been estimated that 13 million people in the United States suffer from cataract.[2] Because of the aging population and their many comorbidities, the importance of understanding the effects of commonly prescribed medications on cataract development is paramount.

Statins are a class of drugs that reduce total cholesterol and low-density lipoprotein cholesterol through inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase.[3] The role statins have in preventing cardiovascular mortality has been established and they are a widely prescribed class of medications.[4,5]

Although there are clear benefits to statin therapy in cardiovascular disease,[4,5] findings from studies that explored the association between statin use and the incidence of cataract have been inconsistent and controversial. Initial concerns arose from an animal study in which statins were found to have a positive dose-response with the formation of cataracts in dogs.[6] However, subsequent human studies have led to variable results: some investigators have confirmed an association between statin use and cataract,[7-10] and others have found either no association,[11-14] a protective effect,[15-17] or a variable effect dependent on patient age and duration of statin use.[18]

In light of the controversy, the objective of the current study was to further explore the influence of statin therapy on the development of cataracts in 2 large North American populations.

Methods

Study design

A nested case-control study approach was applied to 2 different patient populations to determine the effect of statin

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Corresponding author: Dr G.B. John Mancini, Department of Medicine, Faculty of Medicine, University of British Columbia, 2775 Laurel St, Vancouver, British Columbia, V5Z 1M9, Canada. Tel.: +1-604-875-5477; fax: +1-604-875-5471.

E-mail: mancini@mail.ubc.ca

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Results: For the BC cohort, the crude rate ratio (RR) for use of any statin was 1.30, and the adjusted RR was 1.27 (95% confidence interval, 1.24-1.30). The adjusted RRs for each individual statin were all statistically significant. For the IMS LifeLink cohort, the crude RR for use of any statin was 1.13, and the adjusted RR was 1.07 (95% confidence interval, 1.04-1.10).
Conclusions: This study demonstrates that statin use is significantly associated with cataract requiring surgical intervention. This relationship was consistent in both North American cohorts. Further assessment of this relationship is recommended, especially because of increased statin use and the importance of acceptable vision in old age when cardiovascular disease is common.

Résultats : En ce qui concerne la cohorte de la C.-B., le taux brut (TB) de l'utilisation de toute statine était de 1,30 et le TB ajusté était de 1,27 (intervalle de confiance à 95 %, 1,24-1,30). Les TB ajustés de chacune des statines étaient tous statistiquement significatifs. Pour ce qui est de la cohorte de la IMS LifeLink, le TB de l'utilisation de toutes les statines était de 1,13 et le TB ajusté était de 1,07 (intervalle de confiance à 95 %, 1,04-1,10).
Conclusions : Cette étude démontre que l'utilisation des statines est associée de manière significative à des cataractes nécessitant une intervention chirurgicale. Ce lien était cohérent dans les deux cohortes nord-américaines. D'autres évaluations sur ce lien sont recommandées, particulièrement en raison de l'augmentation de l'utilisation des statines et de l'importance d'avoir une vision acceptable au cours de la vieillesse, soit à cette période où la maladie cardiovasculaire est commune.

use on the risk of cataract and need for surgical intervention and consistency of the findings.

Data sources

The first cohort was derived by linking several data files within the British Columbia (BC) Ministry of Health to create a cohort of subjects who had visited an ophthalmologist from 2000 to 2007. Information on all hospitalizations was obtained through the Discharge Abstract database.[19] All physician visit information was obtained through the Medical Services Plan data file[20] and prescription drug information, including drug strength and dose, was obtained from the BC Ministry of Health and the PharmaNet Stewardship Committee.[21] These databases have been used previously in multiple health services and epidemiological studies.[22,23]

The second cohort was comprised of male subjects aged 40-85 years who were registered in the IMS LifeLink database, a large health claims database in the United States. Information on all physician visits, hospitalizations and prescription drug use from 2001-2011 was obtained.

Approval was obtained for this nested case-control study from the University of British Columbia Behavioral Research Ethics Board.

Cohort description

The BC cohort was comprised of all subjects who had at least one visit to an ophthalmologist in BC from January 2000 to December 2007. Patients entered the cohort on the day of their first visit and were followed until the date they met the criteria for case definition of cataract or termination of the health claim.

The IMS LifeLink cohort was compromised of men aged 40-85 years. Subjects entered the cohort on the first date of any health claim in the database and were followed until the date they met criteria for case definition of cataract or termination of the health claim. Subjects entered the cohort between the years of 2001 and 2011.

Case definition

All newly diagnosed cases of cataracts were identified in both cohorts. A cataract was defined as the first date of an ophthalmologist visit for cataract, and having received a cataract surgical code within a year of the date of this visit, indicating that the subject had received cataract surgery. This was done to ensure that the cataract was clinically significant enough to be eligible for surgical intervention. The date of the first ophthalmologist visit confirming the diagnosis was deemed the index date.

Control selection

A risk-set was created of all subjects in the cohort who had no previous history of a cataract, were of similar age (± 1 year), who entered the cohort during the same month and year as the case and who were followed as long as the index date of the case. For each case, 10 controls were selected at random and matched to the case. This form of control selection, referred to as density-based sampling, ensured that

Table 1. Comparison of characteristics between patients and matched control subjects in the British Columbia cohort

	Cases	Controls	*P*
N	162,501	650,004	
Age, years	73.2 ± 10.5	73.2 ± 10.5	0.3227
Follow-up, years	1.7 ± 1.8	1.7 ± 1.8	0.9974
Male sex, %	41.6	43.9	< 0.0001
Cataract risk factors the year before index, %			
Diabetes	14.0	13.7	0.0036
Hypertension	39.4	34.7	< 0.0001
Glaucoma	16.9	16.3	< 0.0001
COPD	7.5	6.6	< 0.0001
Uveitis	0.9	0.8	0.3790
Cardiovascular disease (MI, stroke)	2.3	2.6	< 0.0001
Antipsychotic	7.1	6.2	< 0.0001
Oral steroids	7.3	6.3	< 0.0001
Inhaled steroids	2.2	2.7	< 0.0001
SSRI	5.0	4.9	0.0117

COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; SSRI, selective serotonin reuptake inhibitor.

Table 2. Comparison of characteristics between patients with cataracts and their matched control subjects in the IMS LifeLink cohort

	Cases	Controls	*P*
N	45,065	450,650	
Follow-up in years	1.9 ± 1.8	1.9 ± 1.8	0.8837
Age, years	71.7 ± 10.3	71.6 ± 10.4	0.0112
Cataract risk factors the year before index, %			
Diabetes	13.5	9.9	< 0.0001
Hypertension	55.2	48.6	< 0.0001
Glaucoma	8.9	6.4	< 0.0001
COPD	14.1	11.0	< 0.0001
Uveitis	0.5	0.2	< 0.0001
Cardiovascular disease (MI, stroke)	3.6	3.3	0.0006
Antipsychotic	0.9	1.2	< 0.0001
Oral steroids	5.3	4.6	< 0.0001
Inhaled steroids	1.8	1.5	< 0.0001
SSRI	6.1	5.4	< 0.0001

COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; SSRI, selective serotonin reuptake inhibitor.

the cases and controls were matched according to follow-up time and calendar time, and thus had the same opportunity to receive a statin drug and incur an adverse effect. This also controlled for temporal variations that might affect prescribing, and also allowed for the odds ratio (OR) to be a close approximation of the rate ratio (RR).[24]

Statistical analysis

Descriptive statistics were used to examine the distribution of cases and controls for both cohorts (Tables 1 and 2). We defined long-term regular users as patients who had received at least 1 prescription for a statin every 3 months in the year before the index date. Because many drug-related adverse events occur in patients who are drug-naive, within the BC cohort long-term users were further grouped into new users (those who had started statin treatment after cohort entry in the year before the index date) or previous users (those who were already taking a statin at the time of cohort entry). Short-term regular users were defined as those who had received at least 1 statin prescription every 3, 6, or 9 months before the index date. Irregular users were defined as those who started using a statin for 3 months, had interrupted use for 3 months and then stopped or resumed use in the year before index date. Finally, patients with diverse statin use were those who had used more than 1 type of a statin every 3 months in the year before the index date.

The statins that were prescribed in the 2 cohorts, and therefore included in analysis, are shown in Tables 3 and 4. There was very minimal use of cerivastatin in the case and control groups, which was discontinued from clinical use in 2001,[25] and therefore it was excluded from analysis.

Using a conditional logistic regression model, crude and adjusted RRs were calculated using variables that potentially influence cataract formation: sex (for the BC cohort), diabetes, hypertension, glaucoma, chronic obstructive pulmonary disease, uveitis, history of cardiovascular or cerebrovascular disease (previous history of stroke or myocardial infarction), and the following prescription drugs: antipsychotics, oral steroids, inhaled corticosteroids, and selective serotonin reuptake inhibitors. Number needed to harm (NNH) was computed by taking the reciprocal of the difference of the incidence rates between the statin users and nonusers.

Table 3. Crude and adjusted rate ratios for use of statin in the British Columbia cohort

			Crude	Adjusted	
	Cases	Controls	Rate Ratio	Rate Ratio	95% CI
Subjects, n	162,501	650,004			
No use 1 year before index, %	78.71	80.59	1.00	1.00	Reference
Long-term regular use of any statin, %	6.47	5.24	1.30	1.27	1.24-1.30
Previous user	4.51	3.75	1.26	1.24	1.20-1.27
New user	1.96	1.49	1.39	1.36	1.30-1.42
Simvastatin	1.49	1.17	1.34	1.31	1.25-1.37
Previous user	1.04	0.83	1.31	1.28	1.21-1.35
New user	0.45	0.34	1.41	1.38	1.27-1.51
Pravastatin	0.60	0.50	1.25	1.22	1.13-1.31
Previous user	0.52	0.44	1.24	1.21	1.12-1.31
New user	0.07	0.08	1.30	1.26	1.04-1.53
Lovastatin	0.33	0.30	1.17	1.14	1.04-1.26
Previous user	0.32	0.28	1.19	1.16	1.05-1.28
New user	0.02	0.02	0.96	0.93	0.60-1.44
Fluvastatin	0.10	0.07	1.43	1.39	1.16-1.66
Previous user	0.08	0.06	1.34	1.30	1.07-1.58
New user	0.01	0.01	2.32	2.24	1.34-3.72
Atorvastatin	3.42	2.78	1.29	1.26	1.22-1.31
Previous user	2.21	1.87	1.24	1.22	1.17-1.27
New user	1.21	0.92	1.39	1.36	1.29-1.43
Rosuvastatin	0.24	0.18	1.46	1.42	1.27-1.59
Previous user	0.13	0.09	1.55	1.50	1.28-1.75
New user	0.11	0.09	1.38	1.34	1.13-1.59
Use of diverse statins	0.29	0.23	1.28	1.26	1.14-1.40
Previous user	0.21	0.17	1.26	1.24	1.10-1.40
New user	0.08	0.06	1.33	1.32	1.08-1.62
Irregular use of any statin	5.94	5.51	1.12	1.11	1.08-1.13
Other use of any statin	8.87	8.66	1.04	1.03	1.01-1.05

CI, confidence interval.

Results

The BC cohort was comprised of 162,501 cases and matched with 650,004 control subjects. Cases were 41.6% male and control subjects were 43.9% male. The average age of both groups was 73.2 years; both groups had average

Table 4. Crude and adjusted rate ratios for use of statin in the IMS LifeLink cohort

			Crude	Adjusted	
	Cases	Controls	Rate Ratio	Rate Ratio	95% CI
Subjects, n	45,065	450,650			
No use 1 year before index, %	61.90	63.68	1.00	1.00	Reference
Regular use of any statin, %	14.33	13.32	1.13	1.07	1.04-1.10
Simvastatin	4.68	4.40	1.12	1.05	1.00-1.11
Pravastatin	1.24	1.15	1.14	1.07	0.98-1.17
Lovastatin	1.07	0.93	1.22	1.14	1.04-1.26
Fluvastatin	0.19	0.18	1.08	1.03	0.82-1.29
Atorvastatin	4.94	4.64	1.12	1.07	1.02-1.12
Rosuvastatin	1.13	1.08	1.10	1.04	0.95-1.15
Use of diverse statins	1.08	0.94	1.21	1.12	1.02-1.23
Irregular use of any statin	9.79	9.36	1.10	1.04	1.01-1.08
Other use of any statin	14.78	13.64	1.13	1.09	1.06-1.12

CI, confidence interval.

follow-up by an ophthalmologist of 1.7 years. These 2 variables were controlled for, and thus were not statistically different. Cases were significantly more likely to have all identified cataract risk factors, with the exception of uveitis, which was similar in both groups (Table 1).

In the BC cohort, the crude RR for cataract formation and surgery associated with regular use of any statin was 1.30, and adjusted for the variables in Table 1, the RR was 1.27 (95% confidence interval [CI], 1.24-1.30). Broken down according to usage, the adjusted RR for new users was 1.36 (95% CI, 1.30-1.42), and for previous users the adjusted RR was 1.24 (95% CI, 1.20-1.27). The adjusted RRs for long-term regular use of each individual statin were all statistically significant, and ranged from 1.14 (95% CI, 1.04-1.26) for lovastatin to 1.42 (95% CI, 1.27-1.59) for rosuvastatin (Table 3).

The IMS LifeLink cohort was comprised of 45,065 cases and matched with 450,650 control subjects. The average age of each group was 71.7 and 71.6 years, respectively; both groups had an average follow-up of 1.9 years. Again, these 2 variables were controlled for, and thus were not statistically different. Cases were significantly more likely to have all cataract risk factors examined (Table 2).

In the IMS LifeLink cohort, the crude RR for cataract formation and surgery associated with regular use of any statin was 1.13; adjusted for the variables in Table 3, the RR was 1.07 (95% CI, 1.04-1.10). The adjusted RRs for individual statins varied within a narrow range from 1.03 for fluvastatin to 1.14 for lovastatin; the adjusted RR was not significantly associated with cataract for pravastatin (1.07; 95% CI, 0.98-1.17), fluvastatin (1.03; 95% CI, 0.82-1.29), and rosuvastatin (1.04; 95% CI, 0.95-1.15), but was significantly associated for simvastatin (1.05; 95% CI, 1.00-1.11), lovastatin (1.14; 95% CI, 1.04-1.26), atorvastatin (1.07; 95% CI, 1.02-1.12), and use of diverse statins (1.12; 95% CI, 1.02-1.23; Table 4).

In the BC cohort the age-adjusted absolute risk for statin nonusers was 15 per 1000 person-years and was 20 per 1000 person-years for statin users. In the IMS LifeLink cohort the age-adjusted absolute risk for statin nonusers was 20 per 1000 person-years and was 24 per 1000 person-years for statin users (Table 5). The NNH in the BC cohort was 200 for 1 year and assuming a constant risk increase, this translates to 40 for a 5-year period. In the IMS LifeLink the NNH was 250 for 1 year and 50 for 5 years (Table 5).

Discussion

Results of this study demonstrated that statin use is associated with a greater incidence of cataract diagnosis leading to surgical intervention in 2 large North American patient populations. The 2 cohorts differed in that the IMS LifeLink cohort represented a general male population, and the BC cohort was a patient population of both sexes who had been referred to ophthalmologists, however, the relationship between statins and cataract was consistent between both cohorts.

Table 5. Age-adjusted absolute risks for statin nonusers and statin users and corresponding 1- and 5-year NNH in the BC and IMS LifeLink cohorts

	Statin Nonusers (Person-Years)	Statin Users (Person-Years)	1-Year NNH	5-Year NNH*
BC cohort	15/1000	20/1000	200	40
IMS LifeLink cohort	20/1000	24/1000	250	50

BC, British Columbia; NNH, number needed to harm.
*Assuming a constant risk increase.

Although the mechanism by which statins might induce cataract are unknown, previous studies have shown increased rate of cataract with inherited defects in enzymes of cholesterol metabolism and also with statin medications.[26,27] It has been hypothesized that statins affect the outer cortical region of the lens where cholesterol biosynthesis is critical to maintain lens transparency and structure.[6] Also, because cataracts might be induced by mechanisms of oxidative stress,[28] it has been suggested that statin's effects on oxidation through mitochondrial effects might increase risk for cataract.[29]

In the BC cohort, regular use of any statin was associated with a significantly greater risk for cataract formation and surgery (adjusted RR, 1.27; 95% CI, 1.24-1.30). This was true for all of the statin types, and for new and previous use of each statin type, with the exception of new use of lovastatin (adjusted RR, 0.93; 95% CI, 0.60-1.44). This was likely secondary to minimal use of lovastatin in the BC cohort.

In the IMS LifeLink cohort regular use of any statin was also significantly associated with cataract and surgical intervention although the adjusted RR was lower at 1.07 (95% CI, 1.04-1.10). Although point estimates of RRs associated with specific statins were similar, only simvastatin, lovastatin, and atorvastatin had a significant association with cataract formation and surgery; all other specific statin analyses were not significant but patients using diverse statins showed a statistically significant association. Accordingly, separate analyses in these 2 cohorts are consistent; both support a significant RR associated with statins in the range of 1.07-1.27 and there is no strong evidence to suggest a difference among the statin types with respect to this association.

The results of the current analysis and previous studies are summarized in Table 6. Leuschen et al. defined statin users as patients who received at least a 90-day supply of statin and found that the risk for cataract diagnosis in statin users compared with nonusers was associated with an adjusted OR of 1.27 (95% CI, 1.15-1.40).[9] Although the magnitude of this association is similar to our findings, our results extend this association by showing it in 2 separate cohorts and by using cataract surgery (not just diagnosis of cataract) as the main outcome. Furthermore, when Leuschen et al. separated secondary cataracts from nonsecondary cataracts, these results were not significant.[9] The current study controlled for causes of secondary cataract thereby providing further support for a statin-specific association. The use of cataract surgery as an appropriate outcome in the current study is supported by an analysis by Lai et al.[10] in an elderly Chinese population, which yielded an adjusted hazard ratio (HR) of 1.20 (95% CI, 1.14-1.27) for cataract surgery among statin users although even short-term use (90 days of statin therapy) was considered.

A large retrospective cohort study by Hippisley-Cox and Coupland found adjusted HRs for cataract formation from 1.24-1.55 in women (95% CIs, 0.95-1.82) and 1.06-1.56 in men (95% CIs, 0.83-1.90) and a 5-year NNH of 33 (95% CI, 28-38).[7] These results are similar to the current study, however the RRs found were somewhat lower, and the 5-year NNH was greater at 40 in the BC cohort and 50 in the IMS LifeLink cohort. In their study, Hippisley-Cox and Coupland

Table 6. Summary of clinical studies to date addressing the statin cataract association

Authors	Study Design	Sample Size	Effect Size
Hippisley-Cox and Coupland[7]	Prospective open cohort study	2,004,692 and 225,995 statin users	Adjusted HRs for cataract formation from 1.25 to 1.40 in women (95% CI) and 1.16-1.56 in men (95% CI)
Machan et al.[8]	Cross-sectional study	6397	Statin use associated with nuclear sclerosis (OR, 1.48; 95% CI, 1.09-2.00) and posterior subcapsular cataract (OR, 1.48; 95% CI, 1.07-2.04)
Leuschen et al.[9]	Retrospective propensity score-matched cohort study	13,626 patients, 32,623 control subjects	Primary analysis, risk for cataract in statin users compared with nonusers associated with OR, 1.09 (95% CI, 1.02-1.17), secondary analyses, adjusted OR, 1.27 (95% CI, 1.15-1.40)
Lai et al.[10]	Retrospective cohort study	13,055 patients, 37,110 control subjects	Adjusted HR for cataract surgery, 1.20 (95% CI, 1.14-1.27; $P < 0.001$)
Harris et al.[11]	Randomized placebo controlled study	621	No adverse effect seen on lens opacity with statin treatment
Smeeth et al.[12]	Population-based case-control study	15,479 patients, 15,479 control subjects	Association between exposure to statins and cataract OR, 1.41 (95% CI, 1.21-1.65), adjusted OR, 1.04 (95% CI, 0.89-1.23)
Schlienger et al.[13]	Retrospective case-control study	7405 patients, 28,327 control subjects	Long-term use of statins not associated with increased cataract risk (adjusted OR, 0.90; 95% CI, 0.50-1.60)
Hermans et al.[14]	Cross sectional study	780	Prevalence of cataract in type 2 diabetes patients treated with and without a statin not statistically significant (19% vs 15%)
Chodick et al.[15]	Retrospective population-based cohort study	180,291	Men aged 45-54 years with statin use > 80% of follow-up days adjusted HR, 0.62 (95% CI, 0.54-0.72), use of statins associated with reduced risk of cataract in men and women aged 45-74 years
Klein et al.[16]	Observational population-based study	1299	Five-year incidence of nuclear cataract was 12.2% in statin users compared with 17.2% in nonusers (OR, 0.55; 95% CI, 0.36-0.84), nonsmokers adjusted OR, 0.40 (95% CI, 0.18-0.90)
Tan et al.[17]	Population- based cohort study	1952	Statin use protective for cataract (adjusted HR, 0.52; 95% CI, 0.29-0.93), but not significantly associated with incident nuclear (adjusted HR, 0.66; 95% CI, 0.35-1.25), cortical (adjusted HR, 0.76; 95% CI, 0.44-1.33), or posterior subcapsular cataract (adjusted HR, 1.47; 95% CI, 0.70-3.08)
Fong and Poon[18]	Retrospective case-control study	13,982 patients and 34,049 control subjects	Long-term use of statins protective against cataract (OR, 0.93; 95% CI, 0.87-0.99), short term use of statins associated with cataract surgery (OR, 1.11; 95% CI, 1.05-1.18)
Current analysis	Retrospective case-control study	BC cohort: 162,501 patients and 650,004 control subjects IMS LifeLink cohort: 45,065 patients and 450,650 control subjects	BC cohort adjusted RR, 1.27 (95% CI, 1.24-1.30) and IMS LifeLink cohort adjusted RR, 1.07 (95% CI, 1.04-1.10)

BC, British Columbia; CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, rate ratio.

adjusted for smoking, a known risk factor for cataracts, however this was not possible and is a limitation of the current study. Hippisley-Cox and Coupland identified subjects with cataract based on a diagnosis code, and the current study used a cataract surgical code. Because of the current study's surgical diagnosis and no adjustment for smoking, the higher NNH and lower RRs compared with those of Hippisley-Cox and Coupland, suggest a somewhat decreased effect of statin on cataract formation compared with that demonstrated by Hippisley-Cox and Coupland.[7] Similar to the current study, Hippisley-Cox and Coupland also found no evidence of a dose-response relationship or difference among different types of statins.[7] Another retrospective study of 6336 patients showed that statin use was associated with nuclear sclerosis

(adjusted OR, 1.48; 95% CI, 1.09-2.00) and posterior subcapsular cataract (adjusted OR, 1.48; 95% CI, 1.07-2.04).[8]

In contrast to these concordant studies, there have been studies that have shown no effect of statins on the formation of cataract. In a case control study of 7405 cases and 28,327 control subjects matched according to age, sex, practice, calendar time, and number of years recorded in the medical history, it was found that statins were not associated with increased risk of cataract (adjusted OR, 0.9; 95% CI, 0.5-1.6).[13] However, the upper bound of the CI was consistent with a 60% increase in the risk of cataract, suggesting a potentially insufficient power in the study. Also, only prevalent users were examined, which might have biased results toward a null effect.

A few studies have found statin use to be protective against cataract.[16,17] A prospective observational study of 1299 subjects found that the incidence of cataract was lower in nonsmoking statin users without diabetes and adjusted for age, hyperlipidemia, and sex (adjusted OR, 0.40; 95% CI, 0.18-0.90).[16] However, statin use was ascertained only according to patient interviews. Moreover, subjects who were not adherent to statin use throughout the study were selected out and only a few patients with cataracts (7%) were still taking a statin during all 3 visits compared with 17% of subjects with cataracts who were not taking a statin.[16] This suggests the presence of selection bias which might have contributed to the purported protective association with statin use.

Finally, there have been studies that report inconsistent variable effects. In a retrospective cohort of 180,291 new statin users it was found that among men aged 45-54 years with regular statin use, statins were protective against cataract formation (HR, 0.62; 95% CI, 0.54-0.72), however among women 75 of age and older, regular statin use ($>$ 80% of days) was associated with increased risk for cataract (HR, 1.34; 95% CI, 1.17-1.53).[15] In a case control study, statin use for $>$ 5 years was protective against cataract surgery in patients aged 50-64 years, however, statin use for $<$ 1 year was associated with increased risk for cataract surgery.[18] The biologic plausibility of these findings is unclear. Moreover, statin use was defined as 1 filled prescription in each year before the diagnosis of a cataract, the method of control selection was not clear, and cases and controls were not matched according to calendar time, which could explain the apparent temporal differences in the risk of cataracts with statin use.[18]

This study is not without limitations. Statin use in both cohorts could only be assessed according to prescription drug dispensation in the PharmaNet database and the IMS LifeLink database. Also, cataract surgery was used as a marker of the clinical significance of the cataract, but there was no way to ensure the severity of the cataract or ensure uniform clinical decision-making that deemed the cataract a surgical problem. However, it is important to note that surgical indication is based on Canadian Ophthalmological Society guidelines that recommend surgery when visual acuity decreases to below legal standards for activities, including driving;[30] similar practice guidelines are in place in the United States. It was not possible to adjust for the risk factor of smoking.[7] Last, as in all nonrandomized studies, the effects of unknown confounding variables cannot be calculated or adjusted.

In conclusion, this study found statin use to be significantly associated with increased risk for cataract leading to surgical intervention. This relationship was consistent in 2 separate cohorts from North America and further supports similar observations from several other analyses. Further assessment of the clinical effect of this relationship is recommended, especially in light of increased statin use for primary prevention of cardiovascular disease and the importance of acceptable vision in old age when cardiovascular disease is common. Future studies that address the possible underlying mechanisms to explain this association are also warranted. However, because the RR is low and because cataract surgery is effective and well tolerated, this association should be disclosed but not be considered a deterrent to use of statins when warranted for cardiovascular risk reduction.

Disclosures

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