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Statin use and the Risk of Age Related Macular Degeneration in a Large Health Organization in Israel

Varda Shalev1,2, Miri Sr01, Inbal Goldstein1, Ehud Kokia1, and Gabriel Chodick1,2

1Maccabi Healthcare Services, Tel Aviv, Israel, 2Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel and 3Ha’Sharon Hospital, Golda Campus, Rabin Medical, Petach-Tiqva, Israel

ABSTRACT

Objective: To investigate the association between persistent use of statins and the risk of age-related macular degeneration (AMD).

Design: A population-based retrospective cohort among adults who began statin therapy between 1998 and 2006 in a large health organization in Israel. The organization’s central computerized databases were used to collect data on incident AMD cases diagnosed by ophthalmologists.

Results: A total of 108,973 individuals aged 55 or older were identified. During the study follow-up period 409,113 person-years, there were 2,732 incident AMD cases (6.68 per 1,000 person-years). The crude incidence density rate of AMD among patients at the lowest quintile of persistence with statins (7.18 per 1,000) was comparable to that of highest persistence quintile (7.13 per 1,000). After adjustment for potential confounders, patients in the highest quintile of persistence with statins had a hazard ratio of 0.99 (95% Confidence Interval: 0.78–1.26) for AMD compared with patients in the lowest proportion of days covered (PDC) quintile.

In addition to age, AMD was found to associate with past smoking, asthma, diabetes and frequent visits to ophthalmologists or primary physicians prior to index date.

Conclusions: Our study agrees with previous studies that showed no association between persistent use of statins and reduced risk of AMD. These results suggest that the early reports on a strong protective effect of statins against AMD development were probably a result of a small study effect.

Keywords: Statins, AMD, Persistence, Israel, Visual impairment

INTRODUCTION

Visual impairment is a major health problem for the elderly as it significantly impairs functional status and quality of life and increases the rate of falls and hip fractures. In developed countries, age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people aged 50 years or above.2,3 In the United States, AMD affected 1.75 million people in 2000, and is projected to affect almost 3 million people in 2020.5,7

Studies from several Western countries indicate that the prevalence of AMD in people aged 55 or above is 1.6%,7 increasing with age up to 13.1% at age 84 or older. The prospective Rotterdam Study found that the incidence of AMD is 1.8 per 1,000 person-years in subjects aged 55 years or older.6 Similar annual incidence rates of late AMD were calculated over a long follow-up period in the Blue Mountains Eye Study (2.4 per 1000)6 and in the Beaver Dam Eye study (2.0 per 1000).9

AMD is a degenerative disease of the central portion of the retina (the macula) that results primarily in loss of central vision that is required for most of daily activities. AMD is classified as dry (atrophic) or wet (neovascular or exudative) for clinical purposes. Untreated dry AMD, vision loss is slow, gradual, and is usually associated with moderate visual impairment. In contrast, wet AMD is characterized by a rapid distortion and loss of central vision over a period of weeks to months. Wet AMD comprise 10–15% of AMD cases, but accounts for more than 80% of cases with severe visual loss or legal blindness. The pathogenesis of dry AMD is unclear. Abnormalities in components of Bruch’s membrane have been suggested as well as inflammation and chronic infection.10-15 The molecular
mechanisms involved in wet-AMD are choroidal neovascularization that is controlled by a dynamic balance between properties that either promote or inhibit blood vessel development.\textsuperscript{16,17}

In addition to age, a variety of clinical risk factors for AMD have been identified\textsuperscript{18} including cigarette smoking, cataract surgery, and cardiovascular disease, as well as specific genotypic polymorphisms (e.g., in the complement factor H gene or CPH) that predispose to AMD and interact with other risk factors.\textsuperscript{19} The importance of genetic polymorphisms and gene activation suggests that local inflammation may have a role in the development of AMD. This is further supported by the Women’s Health Study and the Rotterdam Study\textsuperscript{20,21} that reported on significant association between high sensitive CRP and the risk of AMD.

Statins, or HMG co-A reductase inhibitors, a group of lipid lowering drugs, have been found to have some beneficial pleiotrophic effects that include anti-inflammatory, antithrombotic, and vascular properties.\textsuperscript{22-26} The potential role of inflammation and chronic infection in AMD pathogenesis raised the hypothesis that persistent use of statins may be associated with a reduced risk of AMD.

\section*{METHODS}

\subsection*{Study population}

We conducted this historical prospective cohort study among the members of Maccabi Healthcare Services (MHS), a 1.8-million enrollee Health Maintenance Organization (HMO) operating in Israel. All data were obtained from MHS automated databases that have previously been described and were used to elicit information on all dispensed community prescriptions, hospital discharge data, and biochemistry results, using a unique 9-digit national identification number.

\subsection*{Study outcome}

Incident cases of AMD were defined by the date of first diagnostic codes associated with AMD during the study follow-up period, according to the International Classification of Diseases (ICD-9) code (360.5) and indicated by the diagnosing ophthalmologist. Since detailed clinical data (e.g., retinal pigment epithelial depigmentation, size and type of drusen, etc.) were unavailable, no distinctions were made between early and late AMD.

\subsection*{Cohort definition}

The study cohort has been previously described.\textsuperscript{27} Briefly, the cohort covered the period 1998–2007 and included new users of statins aged 18 or older who from January 1, 1998 to December 31, 2006 had at least one dispensed prescription of 3-hydroxy-3-methylglurulary coenzyme A (HMG-CoA) reductase inhibitors (e.g., lovastatin, pravastatin, simvastatin, atorvastatin). The date of first purchased statin was defined as the index date. We only included patients who were enrolled in MHS and did not have a statin prescription at least 3 years prior to the index date. Also excluded were patients who had been diagnosed with AMD prior to the index date or within one year after the index date.

\subsection*{Proportion of days covered}

We calculated the mean proportion of days covered (PDC) by dividing the quantity of statins dispensed by the total time interval from index date to death, leaving MHS, or July 1, 2007, whichever occurred first.\textsuperscript{28,29} The maximum follow-up was therefore approximately 9.5 years.

\subsection*{Other study variables}

Demographic variables at index date included baseline values of age, gender, marital status, place of residence, and years of stay in Israel (for new immigrants). Socioeconomic level was categorized into quintiles according to the poverty index of the member’s enumeration area, as defined by the 1995 national census. The poverty index is based on several parameters including household income, educational qualifications, crowding, material conditions, and car ownership.\textsuperscript{30} Study subjects’ electronic medical records were reviewed for a diagnosis of chronic conditions such as chronic obstructive pulmonary disease (COPD), morbid obesity, Alzheimer’s disease, and asthma. Diabetes mellitus patients were identified by using the MHS computerized diabetes mellitus patient registry.\textsuperscript{31} Information on cancer history was provided by the Israel National Cancer Registry (INCR) that has collected information of diagnosed cancer cases from all medical institutions in Israel since 1960.

Information on health services utilization, such as number of hospitalizations in general hospitals, visits to outpatient clinics, and filled prescriptions of anti-hypertensive drugs and diuretics, were based on data collected for the year prior to the index date. Laboratory test results included the median of all LDL-cholesterol and included new users of statins aged 18 or older who from January 1, 1998 to December 31, 2006 had at least one dispensed prescription of 3-hydroxy-3-methylglurulary coenzyme A (HMG-CoA) reductase inhibitors (e.g., lovastatin, pravastatin, simvastatin, atorvastatin). The date of first purchased statin was defined as the index date. We only included patients who were enrolled in MHS and did not have a statin prescription at least 3 years prior to the index date. Also excluded were patients who had been diagnosed with AMD prior to the index date or within one year after the index date.

\subsection*{Lipid lowering pharmacotherapy}

Based on previous clinical trials,\textsuperscript{32-35} statin therapy was categorized into three relative efficacy levels that were
created based on expected amounts of LDL-cholesterol reduction from baseline: (a) low efficacy (≤ 30% LDL reduction): daily dose of fluvastatin ≤ 40mg, pravastatin ≤ 40mg, simvastatin ≤ 10mg, cerivastatin 0.2mg, or lovastatin ≤40 mg or 10mg twice daily, (b) moderate efficacy (31–40% LDL reduction): daily dose of fluvastatin 80mg, cerivastatin 0.3mg or 0.4mg, rosuvastatin ≤10mg, simvastatin 20mg or 40mg, atorvastatin 10mg, or (c) high efficacy (≥ 41% LDL reduction): simvastatin 80mg, atorvastatin ≥20mg, rosuvastatin ≥10mg, pravastatin 80mg, or lovastatin 80mg).

Statistical analysis

Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables were performed to determine significant differences in baseline characteristics between PDC levels. Cox regression with years of follow-up as the time scale was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) and to identify variables significantly associated with increased risk of AMD. The full multivariate model included the following baseline values: age at baseline (in 1-year intervals), socioeconomic level, presence of chronic co-morbidity, utilization of health services, and efficacy of the initial statin therapy. Analyses were stratified by age categories. The proportional hazard assumption was tested based on Schoenfeld residuals regressed on follow-up-time.

The study protocol was approved by the Assuta hospital institutional review board.

RESULTS

After applying the inclusion and exclusion criteria, a total of 108,973 individuals were identified as being newly

<table>
<thead>
<tr>
<th>TABLE 1 Study population characteristics*, according to quintiles of proportion of follow-up days covered with statins.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of follow-up days covered with statins</td>
</tr>
<tr>
<td>N=</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Age Mean</td>
</tr>
<tr>
<td>SD</td>
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<tr>
<td>Sex Men</td>
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<tr>
<td>Socioeconomic Mean level</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>LDL-cholesterol&lt;130 (mg/dl)*</td>
</tr>
<tr>
<td>130–159</td>
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<tr>
<td>160–189</td>
</tr>
<tr>
<td>≥190</td>
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<tr>
<td>Missing data</td>
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<tr>
<td>Co-morbid Obesity</td>
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<td>DM</td>
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<td>Cancer</td>
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<td>Hypertension</td>
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<td>Past</td>
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<td>Never</td>
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<td>≤7</td>
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<td>8–12</td>
</tr>
<tr>
<td>13–19</td>
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<tr>
<td>20–29</td>
</tr>
<tr>
<td>≥30</td>
</tr>
<tr>
<td>BMI (kg/m²) Mean</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Statin efficacy Low</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>High</td>
</tr>
</tbody>
</table>

*In the year prior to Index date. SD, standard deviation; BMI, Body mass index.
TABLE 2 Incidence density rates (IDR) of AMD according to the proportion of days of follow-up covered (PDC) with statins, Maccabi Healthcare Services 1998–2007.

<table>
<thead>
<tr>
<th>PDC with statins</th>
<th>Follow-up</th>
<th>Person-years at risk</th>
<th>AMD cases</th>
<th>IDR per 1000 person-years</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest quintile</td>
<td>4.23 (2.33)</td>
<td>70,290</td>
<td>505</td>
<td>7.18</td>
<td>6.57–7.84</td>
</tr>
<tr>
<td>2nd quintile (n = 21822)</td>
<td>4.64 (2.51)</td>
<td>79,357</td>
<td>534</td>
<td>6.73</td>
<td>6.17–7.32</td>
</tr>
<tr>
<td>3rd quintile (n = 21796)</td>
<td>4.89 (2.57)</td>
<td>84,987</td>
<td>519</td>
<td>6.11</td>
<td>5.59–6.66</td>
</tr>
<tr>
<td>4th quintile (n = 21792)</td>
<td>5.02 (2.65)</td>
<td>87,778</td>
<td>556</td>
<td>6.33</td>
<td>5.82–6.88</td>
</tr>
<tr>
<td>Highest quintile</td>
<td>4.97 (2.68)</td>
<td>86,699</td>
<td>618</td>
<td>7.13</td>
<td>6.58–7.71</td>
</tr>
<tr>
<td>Total (n = 108973)</td>
<td>4.75 (2.57)</td>
<td>409,113</td>
<td>2732</td>
<td>6.68</td>
<td>6.43–6.94</td>
</tr>
</tbody>
</table>

* Excluding first year of follow-up.

FIGURE 1 Incidence density rate per 1000 person-years of AMD in the study cohort, by age and sex.

DISCUSSION

Our study results suggest no significant association between persistent statin use and risk of AMD over the follow-up period. Several earlier studies on less than 30 statins users found a protective association between statin use and AMD, which compared statin users and non-users, did not show a significant association between use of statin and reduced risk of AMD, corroborating our findings. Similarly, the recent Complications of Age-related Macular Degeneration Trial (CAPT) study showed that statin therapy does not alter or prevent the progression from early to advanced AMD over a 5-year period. Therefore, the contradictory results can be explained by a “small study effect” (SSE) where small-sized studies are prone to provide overestimated point estimates. In addition, the early studies, which compared statin users and non-users, did not adjust for important confounders, such as cardiovascular risk factors.

The age specific incidence rates of AMD calculated in our study are comparable with previous estimates. For example, in the Beaver Dam Eye Study the 15 year cumulative risk of either early or late AMD in patients aged 65–74 years at baseline (or 80–89 years at end of follow-up) was 31.3%, which is equivalent to an incidence rate of 18 per 1000 per year. This incidence rate is lower yet non-significant hazard ratio of 0.99 (95% CI: 0.76–1.29) was found in the 15 year (Table 3 and Figure 2). Similar results were obtained when analyses were stratified by efficacy levels or different types of statins.

The crude incidence density rate of AMD among patients in the lowest quintile of PDC level (18% or less) was comparable to that of patients in the highest quintile (92% or more): 7.18 per 1,000 (95% CI: 6.57–7.84) vs. 7.13 per 1,000 (95% CI: 6.58–7.71) respectively.

Baseline characteristics associated with increased risk for AMD included age, diabetes, asthma, and frequent visits to ophthalmologists and primary physicians prior to the index date (Table 3). Past smoking was found as a suggestive risk factor ($P = 0.06$).

After adjustment for the variables in Table 3, patients in the highest PDC quintile had a hazard ratio of 1.05 (95% CI: 0.92–1.20) for AMD compared with patients in the lowest PDC quintile.

When analyses were restricted to patients with more than 5 years of follow up, a lower yet non-significant hazard ratio of 0.99 (95% CI: 0.76–1.29) was found (Table 3 and Figure 2). Similar results were obtained when analyses were stratified by efficacy levels or different types of statins.
date. Smoking has been described as a well-established risk factor for AMD in several studies.\textsuperscript{43-45} Smoking was also related with a gradually increasing risk from early to advanced AMD.\textsuperscript{46} The association between smoking and AMD was found to persist even in patients who quit smoking 15 to 20 years ago.\textsuperscript{44,49}

To the best of our knowledge, asthma was never described as risk factors for AMD. This finding can be explained indirectly by a residual confounding of smoking that was unavailable for 20% of the study patients. A recent cross-sectional population-based EUREYE study has indicated that diabetes mellitus is significantly associated with neovascular AMD, but not with geographical atrophy or earlier stages of AMD.\textsuperscript{50} In our study, DM was significantly associated with a small increase in the risk of AMD when analysis was limited to patients with at least 5 years of follow-up, possibly reflecting a larger proportion of neovascular AMD among patients.

Although AMD and cardiovascular diseases (CVD) share many similar risk factors, our study did not detect an increased risk for AMD in patients with a history of CVD. This agrees with many, but not all,\textsuperscript{51} studies that have not demonstrated a consistent association between cardiovascular disease and AMD.\textsuperscript{52-61}

The strengths of the current study include a cohort study design, a systematic and comprehensive collection of personal socio-demographic data, and collection of medical history and utilization of health services prior to the index date, which reduces the possibility for bias due to study outcomes. In addition, our study used internal comparisons among patients who purchased at least one dispensed prescription of statins, which minimizes the threat of confounding by indication.

Nonetheless, some limitations of the study should be considered. Our analysis was retrospective in nature and allocation of statin therapy was not randomized. Despite adjustment for baseline differences, a higher proportion of days covered with statins could still be a surrogate for other unmeasured factors that reflect a higher quality of care and more aggressive treatment.
Our previous study on the present cohort indicated that older age, the presence of chronic diseases, and other risk factors for AMD were more likely to have a higher persistence with statins therapy. Therefore, patients persistent with statins could have been at a-priori higher risk of AMD which could have masked the potential protective effect of statins.

In addition, persistence with statins was estimated according to the number of dispensed medications and calculating proportion of follow-up days covered. Although actual adherence with statins could not be ascertained, we believe that patients who repeatedly purchase statins consume their medication. Also, given the low co-payment for statins for MHS enrollees, purchasing the medication in non-contracted pharmacies is unlikely. In our study we were unable to examine genetic risk factors of AMD. Therefore, we could not assess the potential benefit of statins among patients who may have a genetic predisposition for the development of AMD, such as polymorphisms of CFH, as well as polymorphisms in other genes regulating components of the complement pathway.

In conclusion, we found no evidence to support the association between persistent use of statins and reduction in long-term AMD incidence. We believe that the early studies that suggested a strong protective effect of statins against AMD development, were probably the result of a small sample effect.

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**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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