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Role of Statins in the Development and Progression of Age-Related Macular Degeneration

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Abstract

Purpose—To determine if statins are associated with the development or progression of age-related macular degeneration (AMD)

Methods—A large, national insurance claims database was reviewed to identify individuals age 60 who were enrolled for 2 years and had 1 visits to an eye provider. Prescription claims for statins within a 24 month look-back period and outpatient lipid lab values were also reviewed. Cox regression analysis was used to determine whether statin use was associated with the development of non-exudative or exudative AMD, or progressing from non-exudative to exudative AMD.

Results—Of the 107,007 beneficiaries eligible for the non-exudative AMD analysis, 4,647 incident cases of non-exudative AMD occurred. 792 incident cases of exudative AMD were found among the 113,111 beneficiaries eligible for the exudative AMD analysis. Of the 10,743 beneficiaries with known non-exudative AMD eligible for the progression model, 404 progressed to exudative AMD during their time in the plan. After multivariable analysis, statin use was not associated with the development of non-exudative AMD ($p>0.05$). Statin use of >12 months was associated with an increased hazard for developing exudative AMD ($p<0.005$). Among those taking statins, only enrollees with the highest lipid levels had an increased hazard of developing exudative AMD ($p<0.05$).

Conclusion—In those with elevated lipid levels, >1 year of statin use was associated with an increased hazard for exudative AMD. Lipid status influences the relationship between statins and the risk of AMD.

Keywords

Age-related Macular Degeneration; Claims Database; Statins; Serum LDL; Serum HDL; Serum Triglycerides

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Summary Statement:

Compared to enrollees who were prescribed statins for <6 months, those prescribed statins for >1 year had a higher hazard of developing exudative AMD, but not non-exudative AMD. Lipid status plays an important role in determining the association of statins with the development of exudative AMD.

Background

Age-related macular degeneration (AMD) is a progressive disease affecting central vision and is the leading cause of blindness of people over the age of 65 throughout the Western world.¹ Although anti-VEGF treatments have improved the outcomes of those with the exudative form of the disease, most patients do not regain significant vision^{2,3} thus identifying strategies of preventing the development of AMD and reducing disease progression are of paramount importance. Several cardiovascular risk factors have been associated with the development and progression of AMD including smoking, hypertension and serum lipid status.^{4–9} This suggests that interventions that reduce these risk factors may, in turn, have a positive impact on AMD.

A report by Hall *et al.* (2001) showed a markedly lower rate of exudative AMD among a cohort who reported HMG Co-A reductase inhibitor (“statin”) use.¹⁰ Since that initial report, several other studies have examined the effects of lipid lowering medications on the development of the different forms of AMD, but the results have been inconsistent with some studies showing a negative effect^{11,12}, others no effect^{13–22}, and still others, a beneficial effect^{10,23–28}. Various reasons have been proposed to account for the inconsistent findings, such as small samples sizes, low statin usage rates among study subjects, and grouping of non-exudative and exudative AMD cases together. A major limitation affecting almost all studies, though, is the inability to accurately quantify the amount of statin use by study participants.

The purpose of this study is to use healthcare claims data from a large, national US managed care network that including detailed information on prescription medication usage to test the hypothesis that use of statins is associated with the hazard of developing of non-exudative and exudative AMD and the progression from non-exudative to exudative AMD. We developed three models to test our hypothesis and then performed an additional analysis to test for interactions between lipid levels and the association of statins with AMD.

Methods

Data Source

The i3 InVision Data Mart database (Ingenix, Eden Prairie, MN) contains de-identified records of all beneficiaries in a large managed care network in the United States. We analyzed the subset of beneficiaries who had a claim for one or more International Classification of Diseases²⁹ (ICD-9CM) codes representing any eye-related diagnosis (360–379.9), Current Procedural Terminology³⁰ (CPT-4) code for any eye-related visits, diagnostic or therapeutic procedures (65091–68899 or 92002–92499), or any other ICD-9-CM or CPT codes submitted by an ophthalmologist or optometrist from January 1, 2001 through December 31, 2007. For each beneficiary in the sample, we had access to all ocular and non-ocular medical claims (inpatient, outpatient, skilled nursing facility) as well as demographic data (age, sex, race, ethnicity), socioeconomic information (education level, household net worth), and all outpatient medication prescriptions filled during their time in the medical plan. All individuals who were enrolled in the medical plan had full pharmacy coverage during their enrollment. For those beneficiaries who had outpatient lab testing, the dataset contained all of these results as well.

Subjects

All individuals age 60 or older who were in the database for more than two consecutive years and had one or more visits to an eye care provider during their time in the medical plan were identified. Individuals in the medical plan for less than two years and those who

were not in the medical plan continuously from their beginning to their ending date of enrollment were excluded. ICD-9-CM codes were used to determine whether each beneficiary during the course of the study had one or more diagnoses of non-exudative AMD (ICD-9-CM codes 362.50, 362.51, or 362.57), or exudative AMD (ICD-9-CM code 362.52). (Online Table #1). ICD-9-CM codes were assigned to patients by their eye care providers at the time of their visits. National Drug Codes were used to identify statins and other lipid lowering medications prescribed during the study.³¹

Analysis

The University of Michigan Institutional Review Board determined that this study was exempt from requiring IRB approval since the data were completely de-identified.

Participant characteristics were summarized using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Cox regression analyses were performed to assess the association between statins and the development of non-exudative AMD (Analysis 1) and exudative AMD (Analysis 2). To better characterize progression from non-exudative AMD to exudative AMD, a third analysis was also performed on enrollees already diagnosed with non-exudative AMD to assess the association of statin use on the hazard of experiencing disease progression (Analysis 3). To make sure that all the events were incident cases of AMD, all individuals who were diagnosed with the condition of interest (exudative or non-exudative AMD) in the first two years they were enrolled in the plan were excluded from Analyses 1 and 2, respectively and for Analysis 3, those who were diagnosed with exudative AMD during this initial two year period were also excluded. During the two year look-back period we also quantified amount of statins prescribed to each enrollee. In the first two analyses, subjects were followed from an index date (two years after enrollment in the medical plan) until the date of first diagnosis with non-exudative or exudative AMD, the date they left the plan, or the last date we had access to data (Dec 31, 2007). In the third analysis, subjects were followed from the date of diagnosis of non-exudative AMD until they were diagnosed with exudative AMD or until the time they were censored because they left the plan or the last date for which we had data (Dec 31, 2007).

For the regression analyses, the dependent variable for each model was the development of non-exudative AMD, exudative AMD, or conversion from non-exudative to exudative AMD, respectively. Statin use, which was our main predictor variable, was treated as a time dependent covariate in the models. The number of days each beneficiary had covered by a prescription for statins was totaled over a 24 month period for every time point prior to the event (diagnosis of AMD) or censorship (time when the beneficiary left the plan or last date we had data). This total was then divided into the following categories: 0–6, 7–12, 13–18, or 19–24 months of statins out of that 24 month period of time.

In order to understand the associations of statins with AMD controlling for serum lipids, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG) were included in the analysis. As covariates, levels of these lab tests were split into categorical variables using the American Heart Association guidelines for divisions among the various lipid levels.³² For enrollees who had 1 of these outpatient lab values drawn during their time in the plan, every day after the lab value was drawn the patient was considered to have that value until that particular lab test was repeated. For example, if an enrollee had an LDL level recorded as 200mg/dl, she was considered to have that level until her next LDL result of 150mg/dl was recorded which then became her new assigned value.

Interactions were also examined between statin prescriptions and each of the three lipid lab tests (HDL, LDL, and TG), to assess if the association of statins with AMD would be

modified based on the different lipid levels. As not all enrollees had a serum lipid level checked during their time in the plan and others had multiple tests, the individuals included in the Cox regressions were weighted inversely to their probability of having observed lab data to help prevent the introduction of bias by studying only patients who have records of lipid levels and better represent within the model those that did not have lab values drawn. These probabilities were estimated through logistic regression analyses that were performed within all individuals meeting our sample inclusion criteria.³³

In all of the models, age was used as the time axis and controlled for. Each of the regression models were also adjusted for potential confounders including sociodemographic factors (sex, race, education level, household net worth), comorbid ocular conditions (cataract, pseudophakia / aphakia, open-angle glaucoma, diabetic retinopathy) and systemic medical conditions which may be associated with AMD (diabetes mellitus, systemic arterial hypertension, obesity, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, renal insufficiency, coagulopathy, blood loss anemia, deficiency anemias, systemic hypotension, skin cancer (a surrogate measure of long-term sun exposure)), use of lipid lowering medications other than statins, and the number of visits to an eye-care provider. Analyses were performed by using SAS 9.2 (Cary, NC). The Cox regressions determined the adjusted hazard ratios of developing non-exudative AMD, exudative AMD, and conversion from non-exudative to exudative AMD. For all analyses, p values of < 0.05 were considered statistically significant.

Results

A total of 486,124 beneficiaries met the study inclusion criteria (Figure 1). Statin users (n=223,104) were younger (67.9 years vs. 68.5 years for non-users, $p<0.01$) and more likely male ($p<0.01$) than nonusers (n=263,020). After excluding beneficiaries without serum lipid levels and those with non-incident AMD, 107,007 were eligible for the non-exudative AMD analysis, 113,111 were eligible for the exudative AMD analysis and 10,753 who had a known diagnosis of non-exudative AMD during the lookback period were eligible for the progression to exudative AMD analysis. The mean length of time in the plan for those beneficiaries who were eligible was 4.2 ± 1.4 years. Those not included in the 3 analyses because of a lack of lab values were more likely to be older (68.2 years vs. 65.6 years, $p<0.01$), White (75.2% vs. 69.0%, $p<0.01$) and male (45.6% vs. 47.1%, $p<0.01$).

Development of Non-exudative AMD

Of the 107,007 beneficiaries eligible for inclusion in this analysis, 56,630 (52.9%) filled 1 or more statin prescriptions during the period of observation. Among the 4,647 individuals (4.3%) who developed non-exudative AMD during their time in the medical plan, 2,460 (52.9%) were prescribed statins. The average length of time that such individuals took statins during their time in the plan was 751 (± 634) days. When examining statins and lipid levels as independent variables in the Cox regression model, the development of non-exudative AMD was not significantly associated with statin use of any duration ($p>0.05$ for all comparisons). (Table 2) There was also no association between LDL or TG levels and non-exudative AMD. Persons with optimal HDL levels (≥ 60 mg/dl) had a 13% increased hazard of developing non-exudative AMD (adjusted HR=1.13; CI: 1.03–1.25; $p=0.014$) compared to those with low (39 mg/dl or less) levels of HDL.

Development of Exudative AMD

Among the 113,111 enrollees who met the inclusion criteria for this analysis, 59,531 (52.6%) used statins during the observation period. Of the 792 individuals (0.7%) who developed exudative AMD, 455 (57.5%) took statins. On an average, such individuals took

statins for 804 ($\pm$ 641) days. The Cox regression showed that compared to those prescribed statins for $\leq$ 6 months, individuals prescribed statins for 6–12 months had no significant association with developing exudative AMD (adjusted HR=0.99; CI:0.69–1.41, $p=0.952$). (Table 2) Statin use for 13–18 months was associated with a 57% increased hazard for developing exudative AMD and 19–24 months was associated with a 48% increased hazard of developing exudative AMD (13–18 months adjusted HR=1.57; 95% CI: 1.16–2.13, $p=0.003$; 19–24 months adjusted HR=1.48; 95% CI:1.17–1.88, $p=0.001$). Independent of statin use, those with the highest levels of LDL (LDL $\geq$ 190 mg/dl) had an 85% increased hazard of developing exudative AMD (adjusted HR=1.85; CI: 1.07–3.21, $p=0.028$) compared to beneficiaries with optimal LDL levels (<100 mg/dl). Compared to those with low levels of HDL or TG, individuals with high levels of these serum lipids had no increased risk of developing exudative AMD.

Progression from Non-exudative AMD to Exudative AMD

Of the 10,753 persons with non-exudative AMD who were eligible for this model, 5,341 (49.7%) used statins during the look-back period. Among the 404 individuals (3.8%) who progressed from non-exudative to exudative AMD during the study period, 222 (55.0%) took statins. Such individuals took statins for an average of 797 ($\pm$ 649) days. The highest category of statin use, (19–24 months) was associated with an increased hazard for progression from non-exudative to exudative AMD (adjusted HR=1.63; CI:1.16–2.29; $p=0.005$) relative to those using statins for 0–6 months. (Table 2) Compared to those with low levels of HDL or TG, individuals with high levels of these serum lipids had no increased risk of progressing to exudative AMD.

Lipid and Statin Interactions

Analyses 1, 2 and 3 shown above treat statins and lipid values as independent variables in the same model enabling us to study the relationship between each of these factors with AMD while controlling for the others. However, given that the main indication for statin use is to lower lipid levels, additional analyses were performed to determine whether associations between statins and different forms of AMD varied depending on the beneficiary's serum lipid levels. (Table 3) Also, due to small N's of those with the highest levels of TG and LDL in enrollee's taking statins >12 months, these groups were combined into their respective next highest categories. When accounting for these interactions compared to people with similar lipid profiles who used statins for <12 months, those using statins $\geq$ 12 months who had the highest levels of TG (TG >200 mg/dl adjusted HR: 1.20 95% CI: 1.09–1.33) and near optimal levels of LDL (100–129 mg/dl adjusted HR: 1.11 95% CI: 1.00–1.23) had increased hazards for developing non-exudative AMD. In beneficiaries who used statins for $\geq$ 12 months and had an LDL >160 mg/dl were found to have a decreased hazard of developing non-exudative AMD (adjusted HR=0.80 95% CI: 0.64–0.99) as compared to those with LDL >160 mg/dl and <12 months statin use. The hazard of developing exudative AMD or progressing from non-exudative to exudative AMD was increased in people with the highest levels of lipids, regardless of lipid type (HDL, LDL or TG) ($p<0.05$ for all groups). Those with lower LDL levels (<160 mg/dl) trended towards a decreased hazard of developing or progressing to exudative AMD compared to those taking statins for less than 12 months. (Table 3)

Discussion

Statins are the most commonly prescribed drugs in the US and have proven their effectiveness in reducing cardiovascular and cerebrovascular mortality.^{34–36} The current indications for statins continue to expand.^{37–41} As it is thought that many of the underlying pathologic processes that lead to heart disease are also thought to play a role in the

development of AMD^{42–45}, it has been hypothesized that statins might also confer a beneficial effect on AMD. The data available in the literature show variable associations between statins and AMD. Our results show that the effect of statins on AMD development or progression depends on the length of statin use, patients' serum lipid levels, and the type of AMD.

To the best of our knowledge, this is the largest study examining the relationship between duration of statin use, serum lipid levels and the hazard of developing or experiencing progression of AMD. The current literature shows quite variable results when assessing the relationship between statins and AMD. Only one study has shown a significantly increased risk for non-exudative AMD, and one other has demonstrated an increased risk for exudative AMD among statin users.^{11,12} Possible reasons for such disparate findings among the various studies include low usage rates of statins among study participants and researchers classifying different forms of AMD as a single disease in their analysis. In the present analysis, the increased hazard of exudative AMD among statin users was only observed in those who took the medications for > 1 year, a finding that continued to be seen in further analyses in those with the highest lipid levels. Only four previous studies controlled for lab values while studying the association between statins and AMD, one of which²⁵ found a decreased risk of exudative AMD development while the others found no association^{16,18,20}, but none of these studies examined a possible interaction between the two variables. Since much of the existing literature either did not quantify statin use or did not control for serum lipid levels or interactions between these two factors, this may help to explain why many studies in the literature have generated conflicting findings relative to one another.

As is the case with any analysis, confounding variables can play a crucial role in the outcomes of the study. Although many factors can be controlled for, certain biases are more difficult despite researchers' best attempts. Since the primary indication for statin use is elevated lipid levels and both elevated LDL's and statin use over 1 year were independently found to increase the hazard of exudative AMD after controlling for one another in the models, additional analyses were performed to examine the interaction between lipid levels, statin use and development of AMD. In these analyses the groups with highest LDL's and TGs who were prescribed statins for over 1 year had significantly higher hazards of developing or progressing to exudative AMD as compared to those using statins for 6 months or less. Since this combination of variables was associated with an increased hazard for exudative AMD, it is likely that when analyzed independently of each other, this group masked a possible beneficial effect of statin use in beneficiaries with lower LDL levels as seen in the interaction analyses.

The mechanism by which statins and lipid levels are associated with AMD is unclear. Our results imply that these interactions may be different for different groups of people, based in part upon by their serum lipid levels, and may point to novel mechanisms of action that need to be explored. Ultra-structural studies have shown that the lipids within drusen are formed by local intra-ocular production and not by direct serum lipid deposition, but these studies also do not rule out the possibility that serum lipids are an upstream contributor to this process.^{46,47} Also of note, are in vitro studies that suggest an association between LDL and AMD by demonstrating the toxic effects of oxidized LDLs on RPE cells similar to that which occurs in blood vessel walls leading to atherosclerotic changes.⁴⁸ Despite this in vitro pathologic association, it is still unclear how serum oxidized LDL's effect the type and amount of lipids produced within the eye.

A growing body of literature, including several population based studies, have demonstrated an association between elevated HDL levels and the formation of soft drusen.^{8,14,19} Two recent genome-wide assays have also identified a link between alleles of the hepatic lipase

(LIPC) gene that are associated with increased serum HDL and non-exudative AMD.^{49,50} Our finding of optimal HDL levels (< 60 mg/dl) being associated with an increased hazard of developing non-exudative AMD ($p < 0.05$) corroborates that an association between plasma HDL and AMD exists. The effect of statin use on drusen formation is not known and requires further investigation.

Study strengths

First, our database is comprised of a large national sample of insured individuals throughout the United States which allowed for a substantial pool of subjects to be accrued for each of the models. Also by having each beneficiary's sociodemographic profile and detailed claims data on ocular and non-ocular medical conditions, we were able to control for numerous potential confounding variables. In addition, outpatient records enable us to quantify statin use on an almost day-to-day basis. Obtaining medication usage from pharmacy records instead of patient self report eliminates patient recall bias. Lastly, by including lab values we were able to determine which components of hyperlipidemia affected different forms of AMD, independent of statin use.

Study Limitations

Several limitations of this report that need to be acknowledged. First, this study was designed to assess potential associations between independent variables (statins, lipid levels) and dependent variables (forms of AMD) and these relationships cannot determine causation. Further work will be needed to find out if the increased hazard of exudative AMD observed among those prescribed statins was due specifically to statin use, or if statin use was simply a marker for unmeasured confounders. This study also only included patients insured through one managed care network and may not be generalizable to other patient populations who may not have similar levels of access to healthcare services, medications, and lab testing. Also during data analysis despite using a weighted analysis to derive hazard ratios, a large number of enrollees were excluded from the model due to a lack of lab values during their time in the plan. The excluded group was more likely to be older and white, suggesting the inclusion group had a lower overall likelihood of developing AMD, but the true effect of exclusion is incalculable.

Another limitation is the inability to factor important clinical information into our models that are not included in claims databases. For example, our database does not have information on tobacco use, a known risk factor for AMD.⁴⁵ In a similar manner, we are not able to account for use of nonprescription medications such as vitamins. This issue is particularly relevant given suggestions in the literature that antioxidants decrease the efficacy of statins in cardiovascular disease.⁵¹ The interaction of statins and the efficacy of high dose antioxidants and minerals, as used in the Age Related Eye Disease Study, requires further study. Another limitation is the inability to account for geographic atrophy as a separate entity. Typically geographic atrophy is coded as non-exudative AMD and therefore, it is unable to be studied separately from other forms of AMD using claims data. Lastly, because the dataset has been completely de-identified, we are unable to search the medical records to have a trained retina specialist to verify the presence of AMD and ensure it was coded properly or to determine how adherent the beneficiaries were to their prescribed medications.

In summary, our study shows that compared to no or minimal statin use (< 6 months), longer term (> 12 month) use of statins is associated with an increase in the hazard of developing exudative AMD and that serum lipid levels modify the association between statin use and AMD. Further research into this topic is warranted given the implications of this study and the ever increasing number of statin users.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure #1.
Flow chart depicting sample selection criteria for each model

Table 2

Multivariable* Cox regression analyses

	Hazard of Developing Non-exudative AMD Model				Hazard of Developing Exudative AMD Model				Progression From Non-exudative to Exudative AMD Model			
	Hazard Ratio	95% Confidence Limits	p-Value		Hazard Ratio	95% Confidence Limits	p-Value		Hazard Ratio	95% Confidence Limits	p-Value	
Statin Use	REF			REF				REF				
	0–6 months											
	7–12 months	0.93	0.81	1.07	0.324	0.69	1.41	0.952	1.04	0.62	1.75	0.870
	13–18 months	0.99	0.86	1.14	0.886	1.57	1.16	0.003	1.27	0.78	2.06	0.337
	19–24 months	0.97	0.87	1.07	0.515	1.48	1.17	0.001	1.63	1.16	2.29	0.005
LDL Level[†]	REF				REF				REF			
	Optimal (<100)											
	Near Optimal (100–129)	1.03	0.95	1.11	0.544	1.19	0.97	1.45	1.29	0.97	1.72	0.078
	Borderline High (130–159)	0.97	0.88	1.07	0.578	1.27	1.00	1.62	1.50	1.07	2.12	0.020
	High (160–189)	1.08	0.94	1.25	0.282	1.33	0.93	1.91	1.39	0.82	2.36	0.228
	Very High (≥ 190)	1.09	0.84	1.41	0.516	1.85	1.07	0.028	1.41	0.61	3.25	0.423
HDL	REF				REF				REF			
	Low (<40)											
	Average (40–59)	1.06	0.97	1.16	0.199	1.06	0.86	1.32	1.08	0.79	1.48	0.616
	Optimal (≥ 60)	1.13	1.03	1.25	0.014	1.06	0.83	1.35	1.02	0.72	1.45	0.896
Triglycerides	REF				REF				REF			
	Normal (<150)											
	Borderline High (150–199)	0.93	0.85	1.02	0.136	0.83	0.66	1.05	0.77	0.54	1.08	0.133
	High (200–499)	0.96	0.87	1.06	0.412	0.98	0.77	1.23	1.03	0.73	1.43	0.884
	Very High (≥ 500)	0.84	0.32	2.26	0.736	1.16	0.16	8.32	2.33	0.31	17.21	0.408

* Variables controlled for in multivariable analyses: age, sex, race, region of the country, education level, net worth, coagulopathies, skin cancer, iron deficiency anemia, blood loss anemia, renal disease, diabetes, hypertension, cerebrovascular accidents, myocardial infarct, congestive heart failure, peripheral vascular disease, obesity, hypotension, use of other lipid lowering medications, cataract, pseudophakia or aphakia, open angle glaucoma, diabetic eye disease

[†] Enrollees hazard ratios were evaluated by assigning the most recent serum lipid level to that day, then calculating the enrollee's hazard for developing non-exudative AMD, exudative AMD or progressing to exudative AMD on that day.

Table 3

Results of multivariable analysis when examining interaction between lipid levels, statin use and the development or progression of AMD compared to those with similar lipid levels and less <12 months statin use^{*,‡}

Lipid Level in Beneficiaries with >1year statin use	Development of Non-exudative AMD		Development of Exudative AMD		Progression from Non-exudative to Exudative AMD	
	Hazard Ratios	95% Confidence Intervals	Hazard Ratios	95% Confidence Intervals	Hazard Ratios	95% Confidence Intervals
Low HDL (<40) [‡]	1.04	0.95	1.13	0.89	0.88	0.66
Average HDL (40–59)	0.92[‡]	0.86	0.99	1.02	0.90	0.74
Optimal HDL (≥ 60)	0.99	0.91	1.06	1.24[‡]	1.96[‡]	1.58
Optimal LDL (<100)	1.04	0.95	1.14	0.89	0.88	0.66
Near Optimal LDL (100–129)	1.11[‡]	1.00	1.23	0.80	0.54[‡]	0.40
Borderline High LDL (130–159)	1.01	0.87	1.16	0.51[‡]	0.87	0.58
High to Very High LDL (≥ 160)	0.80[‡]	0.64	0.99	1.49[‡]	2.08[‡]	1.29
Optimal TG (<150)	1.04	0.95	1.18	0.89	0.88	0.66
Borderline High TG (150–199)	1.06	0.95	1.18	2.09[‡]	1.80[‡]	1.27
High to Very High TG (≥ 200)	1.20[‡]	1.09	1.33	1.34[‡]	1.54[‡]	1.14
						2.08

* Variables controlled for in multivariable analyses: age, sex, race, region of the country, education level, net worth, coagulopathies, skin cancer, iron deficiency anemia, blood loss anemia, renal disease, diabetes, hypertension, cerebrovascular accidents, myocardial infarct, congestive heart failure, peripheral vascular disease, obesity, hypotension, use of other lipid lowering medications, cataract, pseudophakia or aphakia, open angle glaucoma, diabetic eye disease

[‡] Example of how this chart should be read: A beneficiary with >1 year of statin use and an HDL <40mg/dl had a 4% increased hazard of developing non-exudative AMD compared to a beneficiary with <1year of statin use and a HDL of <40mg/dl

[‡] *p* 0.05