Objective: To investigate whether hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) prevent the development of diabetic retinopathy.

Methods: We conducted a nested case-control study among patients at the Birmingham Veterans Affairs Medical Center, Birmingham, Alabama. Within a study population of male diabetic patients (n=6441), we identified incident cases of diabetic retinopathy diagnosed between January 1, 1997, and December 31, 2001 (n=114). Control subjects were selected using incidence density sampling and were matched for diabetes duration. Information regarding filled statin prescriptions was obtained for cases and controls.

Results: Cases and controls did not differ regarding overall statin use in crude analysis (odds ratio, 1.01; 95% confidence interval, 0.64-1.59) and in multivariate analyses adjusted for age, race, and coexisting medical conditions (odds ratio, 1.00; 95% confidence interval, 0.60-1.67).

Conclusion: The results of this study do not support an association between statins and diabetic retinopathy.

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Diabetes is estimated to cause 40,000 new cases of blindness in the United States each year, and diabetic retinopathy (DR) is directly responsible for most of the cases. In the United States, it is estimated that the prevalences of DR and severe retinopathy are 3.4% (4.1 million persons) and 0.75% (899,000 persons), respectively, in the general population. Duration of diabetes mellitus is the strongest risk factor for DR independent of a patient's age; other recognized risk factors include race, hypertension, and hyperglycemia.

Recent studies suggest that statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) may help prevent the progression of DR. In 2 randomized controlled trials, statins were found to retard the progression of existing DR in patients with hypercholesterolemia and reduce the severity of hard exudates in patients with type 2 diabetes mellitus, clinically significant macular edema, and dyslipidemia. In a small trial, pravastatin was shown to improve retinal hard exudates in all 6 patients at the 1-year follow-up; however, that study had no control group. In a retrospective study, statin use was associated with a delayed onset of vitreous hemorrhage among a group of diabetic patients, most of whom already had DR. The mechanism by which statins might reduce the risk and retard the progression of DR has been postulated to involve lowering cholesterol and serum lipid levels. Other possible mechanisms have been proposed. In 1 study, simvastatin was found to suppress the adhesion of leukocytes to the retinal vessel endothelium and to reduce the number of leukocytes accumulated in the retinal tissue in rats. In another study, cerivastatin was found to block the interaction between advanced glycation end products and their receptors, which is implicated in the development of DR.

These studies provide evidence that statin use may help to retard the progression of DR; however, the potential for statins to prevent the development of DR among diabetic patients has not been assessed in an epidemiologic study. The purpose of this nested case-control study is to evaluate the association between statin use and the risk of developing DR in a cohort of diabetic patients.

D E P I D E M I O L O G Y
METHODS

SELECTION AND DESCRIPTION OF PARTICIPANTS

The Birmingham Veterans Affairs Medical Center (BVAMC), Birmingham, Alabama, is a 134-bed acute tertiary care medical facility and serves as a Veterans Hospital Administration tertiary care referral center for Alabama. All diabetic patients who had at least 1 visit between January 1, 1997, and December 31, 2001, were eligible for study inclusion. Female patients were excluded from analysis because the percentage of women treated in the BVAMC is small and meaningful analyses could not be performed.

The BVAMC provided data files containing demographic information (age, sex, and race) and clinical and medication information for each patient. The clinical file contained a description of each diagnosis made at the BVAMC during inpatient and outpatient visits and the diagnosis date. All diagnoses were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The medication file contained information on each medication prescribed during each patient visit, the prescription date, and the date the prescription was filled. For the clinical and medication files, the information provided pertained to all diagnoses and medications over the course of each patient’s history with the BVAMC and not just those that occurred from 1997 through 2001. No data received from the BVAMC contained information that would allow patients to be identified.

STUDY DESIGN

We identified the study cohort of diabetic patients using the ICD-9-CM code 250 and, within this cohort, a nested case-control study was conducted. Cases of DR were defined using the ICD-9-CM code 362. Information on the diagnosis date of DR was procured, which will hereafter be referred to as the index date. Because the study addresses the association between statin use and the incidence of DR, patients who had a diagnosis of DR before the study period (prevalent cases) were excluded.

Control subjects were selected using incidence density sampling and matched to the cases on diabetes duration.16 To be considered an eligible control for a given case, the control must have had a visit at the BVAMC on or after the index date and must have been free of DR at the time of the visit. Five controls were selected for each case.

The prescription file was queried for the presence of filled statin (atorvastatin calcium, cerivastatin, fluvastatin sodium, pravastatin, simvastatin, or lovastatin) prescriptions. Nonstatin lipid-lowering agents were also extracted from the prescription file. Only those prescriptions that were filled before the index date were considered.

Information on the presence or absence of the following medical conditions was extracted from the clinical data file: ischemic heart diseases (ICD-9-CM codes 410-414), cerebrovascular diseases (ICD-9-CM codes 430-438), lipid metabolism disorders (ICD-9-CM code 272), hypertension (ICD-9-CM codes 401-405), and diseases of the arteries, arterioles, and capillaries (ICD-9-CM codes 440-448). Only diagnoses that were recorded before the index date were considered.

STATISTICAL ANALYSIS

Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between statin use and the development of DR with and without adjustment for age, race, and an array of medical conditions.

RESULTS

A total of 114 cases and 570 matched controls were identified. The distribution of demographic characteristics and coexisting medical conditions among cases and controls is presented in Table 1. There was no difference in the mean age of the 2 groups. The proportion of African American subjects was greater among the cases than the controls, and the percentage of subjects missing information for race was higher among the controls than the cases. Cases and controls did not differ with respect to prevalence of coexisting medical conditions.

When we evaluated cases and controls for aspects of statin use (Table 2), cases and controls did not differ (OR, 1.01; 95% CI, 0.64-1.59), and no association was found after adjusting for race and coexisting medical conditions (OR, 1.00; 95% CI, 0.60-1.67). Compared with nonusers, past users (OR, 0.49; 95% CI, 0.11-2.19) were less likely to develop DR, and those who used statin and nonstatin lipid-lowering medications had a reduced risk (OR, 0.87; 95% CI, 0.37-2.08) compared with those who used neither group of the medications. However, neither of these associations was statistically significant. We found no relationship between duration of statin use and disease risk.

The results of this study suggest no association between statin use and the development of DR. Insufficient sample size is one of the major limitations of the study. Several of the associations suggest clinically meaningful effects, but none of the estimates were statistically significant. Although the point estimate of 0.87 suggests a 13% risk reduction, the analysis was based on 48 patients who took both types of medications, of which only 7 were in the case group. Also, although the OR of 0.49 for past users

<table>
<thead>
<tr>
<th>Comorbid conditions</th>
<th>Cases (n = 114)</th>
<th>Controls (n = 570)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart diseases</td>
<td>38 (33.3)</td>
<td>205 (36.0)</td>
<td>.59</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>9 (7.9)</td>
<td>64 (11.2)</td>
<td>.29</td>
</tr>
<tr>
<td>Lipid metabolism disorders</td>
<td>21 (18.4)</td>
<td>102 (17.9)</td>
<td>.89</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74 (64.9)</td>
<td>340 (59.6)</td>
<td>.29</td>
</tr>
<tr>
<td>Arterial diseases</td>
<td>16 (14.0)</td>
<td>63 (11.1)</td>
<td>.36</td>
</tr>
</tbody>
</table>

aData are expressed as (percentage) of subjects.
suggestions a protective effect, the effect is not statistically significant. The reliability of this estimate is questionable because the analysis was based on a total of 22 past users (2 cases and 20 controls).

Misclassification of cases and controls is another major limitation of this study. The identification of cases was based solely on ICD-9-CM codes and not standardized photographic findings and evaluation of those findings by trained readers. Moreover, it is likely that the diagnoses were made by several different clinicians, each potentially using a different definition of DR. This problem is compounded by the focus on early-stage DR, in which the interpretation of what is and is not DR is less likely to be homogeneous. Thus, although such misclassification represents a very real problem in this study, there is no reason to suspect that it is related to statin use. For the misclassification to bias the results in any direction other than toward the null, the accuracy of DR diagnoses would have to be systematically better for those who did (or did not) use statins. Thus, it is possible that this study failed to document an association due to this bias when such an association truly exists.

Another limitation of the study concerns the categorization of subjects according to aspects of statin use. Subjects were classified as statin users if at least 1 statin prescription was filled at the BVAMC pharmacy. This method might have resulted in the misclassification of patients who had statin prescriptions filled in a pharmacy outside the BVAMC. Duration of statin use was calculated using the date of the first filled prescription and the index date (if patients had records of prescriptions filled after the index date) or the date of the last filled prescription. The patient could have discontinued statin use during that period, and therefore this classification could have led to overestimation of the actual duration of medication use. The effect of statin use on DR in female patients needs to be assessed in other studies. Another issue of concern in this study is left censoring, in that some cases may be prevalent cases and their first records in the BVAMC may not reflect the time when DR was initially diagnosed. The severity of the potential problem is largely alleviated because all eligible cases had to have a prior diagnosis of diabetes mellitus at the BVAMC to be included in the cohort. As a result, all cases in the cohort had had at least 1 previous visit at the BVAMC, and there is a time lag from the diagnosis of diabetes to the diagnosis of DR. In addition, subjects who were diagnosed as having DR before January 1, 1997, were not eligible for the study.

In summary, this study is, to our knowledge, the first to explore the effect of statins on the risk of developing DR in a large cohort of diabetic patients. Previous research consists of case reports or studies regarding the progression of DR in narrowly defined populations. Although previous research has shown that statins help to retard the progression of DR, the results of our study suggest no overall association between statin use and the development of DR. Given the study’s limitations and the observation of several clinically but not statistically significant associations, the results of this study should provoke future research in this area.

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From the Archives of the Archives

The following journals, now defunct, have played more or less important parts in the development of ophthalmology in this country: American Journal of Ophthalmology (1884-1917), Ophthalmic Record (1891-1917), Annals of Ophthalmology (1892-1917), Ophthalmology (1904-1916), Ophthalmic Literature (1911-1922), and American Journal of Physiological Optics (1920-1926). The American Journal of Ophthalmology, an entirely new journal, with an old name and with Edward Jackson as editor, took the place of the three journals discontinued in 1917.