Objective: To compare the incidence rate of hospitalized myocardial infarctions (MIs) and cerebrovascular accidents (CVAs) in subjects with and without neovascular age-related macular degeneration (AMD).

Methods: A retrospective database cohort study was performed in subjects with neovascular AMD and controls matched for age, sex, geography, and enrollment duration. Healthcare claims for the study period from January 1, 2002, to June 30, 2005, were used to identify subjects and outcomes. Incidence of hospitalized MI and CVA events and rate ratios adjusted for 11 risk factors were calculated.

Results: In 7203 subjects with neovascular AMD and 20,208 controls, the rate of MI was 16.2 events per 1000 subjects with neovascular AMD and 23.1 events per 1000 controls. The adjusted rate ratio for MI was 0.58 (95% confidence interval, 0.48-0.72; \( P < .001 \)) for subjects with neovascular AMD vs controls. The rate of CVA was 14.3 events per 1000 subjects with neovascular AMD and 22.1 events per 1000 controls. The adjusted rate ratio for CVA was 0.56 (95% confidence interval, 0.45-0.70; \( P < .001 \)).

Conclusions: Rates of MI or CVA were significantly lower in subjects with neovascular AMD than in controls. These findings could not be explained by systematic differences in case selection, health care use, or comorbidities, although other possible biases cannot be ruled out.

Arch Ophthalmol. 2008;126(9):1280-1286

AGE-RELATED MACULAR DEGENERATION (AMD) is the leading cause of blindness in people 65 years and older in the United States.1,2 Neovascular AMD represents an advanced form of AMD in which choroidal neovascularization develops, and it is associated with severe vision loss if untreated. Population estimates have placed the prevalence of neovascular AMD at 1.3% in adults older than 40 years and 9.3% in people 80 years or older.3 The 10-year incidence of neovascular AMD is 4.1% in persons older than 75 years.4 Several studies have shown atherosclerotic diseases to be a risk factor preceding AMD.5-7 Conversely, 2 studies have prospectively examined the development of new cardiovascular events subsequent to a neovascular AMD diagnosis; neither study identified sufficient subjects with neovascular AMD to provide generalizable results.8,9 Two larger studies in the Medicare population have yielded mixed results.10,11 In this study, a large insurance database was used to estimate and compare incidence rates of myocardial infarction (MI) and cerebrovascular accident (CVA) events in subjects with and without neovascular AMD.

METHODS

DATA SOURCE

The Ingenix LabRx Database (LabRx) contains administrative claims data for an employed, commercially insured population in the United States who are enrolled in 11 health insurance plans affiliated with the United-Health Group. The health plans have contracts with a network of more than 400,000 physicians and more than 50% of all hospitals in the United States to provide health care services. The health plans are geographically diverse, with the largest proportion of patients in the Midwest. Plan members are predominantly from employer-based groups offering plans that include preferred provider organizations, point of service arrangements, or managed indemnity programs. Medical and pharmacy claims are submitted by health care providers to receive payment from the plans for covered services. These claims records are later patient deidentified and aggregated into the research database (LabRx). LabRx con-
Must have ≥2 neovascular AMD diagnoses between July 1, 2002, and June 30, 2005

Figure 1. “Exudative senile macular degeneration” claims had to be coded at least twice on separate dates of service. The neovascular age-related macular degeneration (AMD) index date (X₁) had to have been preceded by a minimum of 183 days of continuous enrollment. Follow-up was censored at either disenrollment or the end of the study period. X₂ indicates the sample subsequent neovascular AMD diagnosis; E₁, the sample event; MI, myocardial infarction; CVA, cerebrovascular accident.

Figure 2. Neovascular age-related macular degeneration (AMD) study cohort identification. The original data set contained 15,046 subjects with neovascular AMD. After 4 exclusion criteria were applied, the remaining 7,203 subjects were included in the study. Forty-three percent of original subjects with neovascular AMD were retained; 15,046 was used as the denominator to calculate the percentages. ICD-9-CM indicates International Classification of Diseases, Ninth Revision, Clinical Modification.

STUDY DESIGN

A retrospective cohort analysis of subjects with neovascular AMD and their matched controls was conducted to determine the incidence of MI and CVA, separately. The study period covered January 1, 2002, through June 30, 2005.

STUDY POPULATION

Subjects With Neovascular AMD

Patients were classified as subjects with neovascular AMD if they had an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of 362.52 (exudative senile macular degeneration) that was coded at least twice on separate dates of service (Figure 1). Retinal specialists were responsible for 94% of the AMD diagnoses coded in this study. The index date was defined as the date of the first neovascular AMD diagnosis coded following a minimum of 183 days of observation. Subjects were included if they were at least 50 years of age at the index date. Since only the year of birth was provided by LabRx, the midpoint (July 1) of the birth year was used as the date of birth for each subject (Figure 2).

Control Subjects

A set of controls frequency-matched on sex, region, enrollment duration, and age at enrollment was identified at approximately an 1:1:1 ratio of controls to subjects with neovascular AMD. Enrollment duration was matched within 6-month intervals, while age was matched within 10-year intervals. Control subjects were excluded if they were coded at any time during the study period for a diagnosis of neovascular AMD or other types of macular degeneration (ICD-9-CM code 362.50 macular degeneration [senile], unspecified; 362.51 nonexudative senile macular degeneration; or 362.57 drusen [degenerative]). From this pool of potential matched controls, 3 subjects were randomly selected without replacement for each subject with neovascular AMD to create the final comparator cohort. Each control subject for a subject with neovascular AMD was assigned the same index date as the corresponding subject with neovascular AMD.

OUTCOMES

Events occurring after the index date were identified using inpatient claims as defined by the variables “place of service” and “health care cost category.” Outcome events with admission and discharge dates that fell on the same day were excluded. Adjacent hospital claims with the same provider identification were counted as a single hospitalization if they were not separated by at least 1 day.

The study outcomes, acute MI and CVAs, were analyzed separately. These outcomes were defined using ICD-9-CM codes for MI (410.xx) and CVA (431.xx, 432.xx, 433.x1, 434.x1, and 436.xx). Outcomes were based on definitions used by the Antiplatelet Trialists’ Collaboration. Subjects were censored at the first event.

To test the positive predictive value (PPV) for the outcomes criteria, 2 hospital physicians working with the research team evaluated 200 (100 subjects with neovascular AMD and 100 controls) randomly selected claims profiles of patients identified with an outcome event. The physicians were shown the specific outcome event claim and then used all available inpatient and outpatient diagnosis, procedural, and pharmacy claims data to determine if the outcome was valid. Reviewers were blinded to the study design and all claims for eye disorders or procedures were redacted from the profiles to remove any possibility of bias based on the inclusion criteria. Where their conclusions differed, a third physician (J.K.J.) evaluated those profiles to make a final decision. Sensitivity analyses were then performed on the results of the discordant claims to obtain a PPV range. The PPV was 71% for MI (range, 47%-75%) and 66% (range, 47%-85%) for CVA. The percentage of agreement between reviewers was 72% (95% confidence inter-
incidence of MI: overall rates

The rate of MI events was lower in the neovascular AMD cohort than in controls. There were 117 MI events in the neovascular AMD group, for a rate of 16.2 MI events per 1000 persons (95% CI, 13.5-19.4). In the control group, 467 subjects had MI events, for a rate of 23.1 events per 1000 persons (95% CI, 21.1-25.2).

DATA ANALYSIS

For each subject, MI or CVA events were recorded along with time to event, end of eligibility, or end of study period expressed to the nearest day. Event rates and 95% CIs were calculated for each outcome by age and sex as the number of events per 1000 persons. Time to event was calculated for each patient as the time from the index date to the outcome date, the date at the end of their eligibility period, or the date at the end of the study period. The detection of either outcome after the index date was counted as an event. Initial data evaluation was performed using SAS software version 9.1 (SAS Institute, Cary, North Carolina).

Cox regression was performed to analyze the difference in time to outcome events between subjects with neovascular AMD and controls (R version 2.4.1; R Foundation for Statistical Computing, Vienna, Austria). Adjustments were made for the presence of risk factors for MI and CVA during the 183-day period preceding the index date, with all covariates included in the model. These risk factors included history of MI or CVA in the 6-month period prior to the index date, congestive heart failure (inpatient only), diabetes mellitus, cardiac arrhythmia (inpatient only), other cerebrovascular diseases, hypertension, hyperlipidemia, heart disease (coronary artery disease), and angina. In addition, the Charlson comorbidity score, a weighted index that takes into account the seriousness of the comorbid conditions, was used to assess comorbidities in the analysis. The Charlson Comorbidity Index was developed as a method for estimating the risk of death from comorbid disease. In this study, a comorbidity score was calculated by modifying the Charlson Comorbidity Index to include corresponding ICD-9-CM codes for most comorbid conditions while excluding codes for MI and CVA. This comorbidity score was included as a continuous variable in the regression model. Rate ratios (R) with 95% CIs were reported.

RESULTS

After applying the selection criteria, 7203 subjects with neovascular AMD with 11128 person-years (PY) and 20280 controls with 28407 PY were identified for analysis. The average enrollment duration was 2.8 and 2.9 years for subjects with neovascular AMD and controls, respectively, with the largest proportion of follow-up time found in patients aged 70 to 89 years. The mean age was 75 years and the ratio of women to men was 3 to 2. Subjects with neovascular AMD had slightly more comorbidities than controls, as indicated by comorbidity scores of 2 or higher for 42.6% and 37.9% of subjects with neovascular AMD and controls, respectively. In the 183-day period prior to the index date, the common comorbid conditions identified in both groups were essential hypertension, disorders of lipid metabolism, diabetes mellitus, and osteoarthritis. A higher proportion of each condition was found in the neovascular AMD cohort than in the control cohort (Table 1).

In general, concomitant drug use in the preindex and postindex periods was similar in subjects with neovascular AMD and controls. Among the top 10 drug classes in both groups were 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, antihypertensive agents, opioid analgesics, proton pump inhibitors, and cyclooxygenase 2 inhibitors. The proportion of users within any drug class was higher in the neovascular AMD group than in controls (Table 1).
Rates of MI were lower in subjects with neovascular AMD than in controls for both sexes. Compared with controls, the risk of MI was 32% lower in men with neovascular AMD and 28% lower in women. Within either group, rates were higher in men than in women. Rates of MI were higher in patients older than 75 years compared with younger subjects; about 70% of both cohorts were older than 75 years (Figure 3).

After adjustment for risk factors and comorbidity scores, the rate of MI events after the index date was 42% lower in the neovascular AMD group than in controls (adjusted RR, 0.58; 95% CI, 0.48-0.72; P < .001). The diagnoses of diabetes, hypertension, heart disease, and angina were significant positive predictors of MI in the regression model. However, the presence of hyperlipidemia was inversely associated with MI (adjusted RR, 0.81; 95% CI, 0.67-0.97; P = .02) (Table 2).

**INCIDENCE OF CVAs: OVERALL RATES**

The rate of CVA events was also higher in controls than in the neovascular AMD cohort. There were 103 CVA events in the neovascular AMD group, for a rate of 14.3 CVA events per 1000 persons (95% CI, 11.7-17.3). In the control group, there were 446 CVA events, for a rate of 22.1 events per 1000 persons (95% CI, 20.1-24.2). The data were stratified by the history of CVA in the 183-day period preceding the index date. Relatively few subjects in either group had a history of CVA.

The rates of CVA were also lower in the neovascular AMD group for both sexes. In particular, the risk of CVA in subjects with neovascular AMD was 37% and 34% lower for men and women, respectively. Again, rates of CVA were higher in patients older than 75 years than in younger subjects (Figure 4).

After adjustment for risk factors, the rate of CVA events after the index date was 44% lower in the neovascular AMD group than in controls (adjusted RR, 0.56; 95% CI, 0.45-0.70; P < .001). Positive predictors in the regression model included history of CVA, diabetes, hypertension, and increasing Charlson score. As with the acute MI outcome, the presence of hyperlipidemia was inversely associated with the development of CVA (adjusted RR, 0.70; 95% CI, 0.57-0.86; P = .001) (Table 3). For both outcomes, few subjects in either cohort had multiple events. A sensitivity analysis excluding these subjects was conducted and results were generally not different from the overall analysis.

**COMMENT**

In this retrospective database study, the adjusted risk of MI and CVA showed a significantly lower rate of events as defined by claims for inpatient health care use in patients with neovascular AMD compared with controls.
These results were consistent within age groups, sex, and history of the defined outcomes. In addition, the results were sustained after adjustments for risk factors. A greater difference in event rates was seen in subjects older than 75 years, who composed a majority of both cohorts. This may be an indicator of the overall health of the 2 cohorts; however, the sample size of subjects younger than 75 years provides low power for interpretation of these results. Biologically, the results appear unexpected given that atherosclerosis has been proposed as a precursor for neovascular AMD, MI, and CVA.5,14,15

The health status of the neovascular AMD cohort appears to be comparable with the general population of a similar age group. Hypertension was found in 49.0% vs 52.4% nationally and diabetes, in 16.5% vs 17.3% nationally (Table 1).19 The prevalence was lower in the control group where 40.3% had hypertension and 15.5% had diabetes. This difference in the rate of chronic diseases is also reflected in the lower comorbidity scores of the control group.

It is possible that the subjects with neovascular AMD received more general medical care because of their eye condition or because they had more chronic disease (supported by higher modified Charlson comorbidity scores in the neovascular AMD group). We examined the frequency of nonophthalmology office visits during the 183-day preindex period and found that 32% of subjects with neovascular AMD made office visits 3 or more times in this period vs 48% of controls. Thus, the control group sought more medical care even though they had lower Charlson scores. Subjects with neovascular AMD also may have received more drug treatment for the risk factors of MI and CVA. But pharmacy claims showed only minor differences in the use of cholesterol medications, antihypertensives, antidiabetics, or antiplatelet agents. However, the possibility that the AMD group may have benefited from better drug therapy management cannot be ruled out (ie, rigorous monitoring and adjustment for compliance, appropriate dosing, or better safety assessment).

In this study, the covariate hyperlipidemia was inversely related to the development of MI or CVA in the neovascular AMD group (Table 2 and Table 3). This may reflect a yet unexplained relationship; however, some evidence suggests AMD is associated with elevated high-density lipoprotein cholesterol levels, a protective factor against MI and CVA.15,17 Hyman and colleagues17 reported that high-density lipoprotein cholesterol levels were 2.3 times more likely to be present in patients with neovascular AMD than controls. Both cohorts received lipid-lowering medication at about the same proportion. For example, HMG-CoA use was 22.1% in subjects with neovascular AMD and 19.5% of controls in the preindex period. But the claims data do not reveal the relative impact of the treatments; thus, the AMD group may have been subject to more effective lipid lowering and possibly have fewer cardiovascular events. Laboratory measures were not available in the database to examine the possible effect of cholesterol on the outcomes.

Wong and colleagues8,18 published 2 studies looking at the risk of CVA and coronary heart disease in patients with AMD. The 10-year risk for developing either outcome was higher in subjects with early AMD than in controls. However, the study identified only 10 and 15 subjects with late AMD in each study, making interpretation difficult for this group.

Duan and colleagues19 conducted a cross-sectional cohort study using Medicare data involving 32 788 subjects with neovascular AMD and yielded different results than our study. Subjects without a prior MI were followed up for 2 years for incident MI events. Subjects with neovascular AMD were 26% more likely to develop MI events than subjects without AMD (95% CI, 1.20-1.33). There were a number of differences compared with our study. The inclusion criteria for neovascular AMD and the definition of an MI were less specific, and no adjustments were made for differential follow-up time between the cohorts or multiple confounding risk factors.

Another study using Medicare data found no difference in the rates of cardiovascular or cerebrovascular events in subjects with neovascular AMD and controls. Alexander and colleagues11 evaluated 15 771 subjects with new-onset neovascular AMD against controls matched for age, race, sex, and follow-up time. No difference was found in overall rates of inpatient MI, ischemic stroke, or combined strokes. This study differed from ours in that it selected subjects with new-onset neovascular AMD while the current study included subjects with new and existing neovascular AMD. No adjustments were made for risk factors to the outcome in this study.

Several limitations should be considered when interpreting the study results. Subject selection was made using a specific ICD-9-CM code for neovascular AMD. However, a nondifferential misclassification is possible in the selection of cohorts or identification of outcomes, which may bias the results toward the null. Efforts were made to minimize this possibility through the requirement of

**Table 3. Adjusted Rate Ratio for the Development of CVAs in Subjects With and Without Neovascular AMD (July 1, 2002–June 30, 2005)**

<table>
<thead>
<tr>
<th>Reference Exposure</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neovascular AMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.65 (0.53-0.81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.56 (0.45-0.70)</td>
<td></td>
</tr>
<tr>
<td>Covariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>0.90 (0.55-1.44)</td>
<td>.65</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>1.31 (0.86-2.00)</td>
<td>.22</td>
</tr>
<tr>
<td>Charlson score</td>
<td>1.08 (1.01-1.15)</td>
<td>.02</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.87 (0.53-1.40)</td>
<td>.56</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.44 (1.16-1.80)</td>
<td>.001</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1.06 (0.85-1.34)</td>
<td>.59</td>
</tr>
<tr>
<td>History of acute MI</td>
<td>0.89 (0.41-1.95)</td>
<td>.77</td>
</tr>
<tr>
<td>History of CVA</td>
<td>3.02 (2.24-4.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.70 (0.57-0.86)</td>
<td>.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.49 (1.24-1.79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other cerebrovascular disease</td>
<td>1.43 (0.92-2.22)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 2.

a Outcome adjusted for presence of angina, cardiac arrhythmia, Charlson score, congestive heart failure, diabetes, heart disease, history of acute MI, history of CVA, hyperlipidemia, hypertension, and other cerebrovascular disease.

b History of acute MI and CVA use the outcome codes to identify events in the 183 days prior to the index event.
the presence of 2 claims for ICD-9-CM code 362.52, which carries high specificity for neovascular AMD and is not shared with any other eye condition. In addition, nearly all diagnoses (94%) were made by a specialist. Control patients were also excluded if other macular disorders that may progress to neovascular AMD were diagnosed.

Variables such as race/ethnicity, smoking, exercise, or diet were not available for analysis. In particular, smoking has been linked to neovascular AMD, heart disease, and stroke.19-23 Other studies have shown a higher prevalence of neovascular AMD among white individuals than black individuals, but black individuals were more likely to develop MI or CVA.24 According to the 2005 US Census Bureau, about 81.5% of people older than 45 years were white.24 Among individuals without diabetes older than 50 years, Centers for Disease Control and Prevention data from the 2002 National Health Interview Survey show that 74.4% (95% CI, 60.8%-88.1%) of patients with macular degeneration were white.25 Thus, the observed and expected proportions are not markedly different and variations in race distribution between patients with neovascular AMD and controls are not likely to have a significant impact on the outcomes. Smoking, exercise, or dietary habits may be different between the cohorts in this study and the impacts of these variables on the outcomes are unknown.

As with all claims studies, limitations exist in the reliability of the ICD-9-CM codes selected to detect events. In published analyses of ICD-9-CM–coded MI events, PPVs of 87% to 97% have been reported when validated by medical record reviews, denoting a high specificity of the outcome when it is coded.26-31 Cerebrovascular accident–coded events in the literature have shown a wider PPV range from 62% to 92%.27,32-36 The claims profile review in this study resulted in PPVs of 71% for MI and 66% for CVA. Claims profiles and not medical records were reviewed by 3 physicians in this study. Lower PPVs and interrater agreement are expected since claims data do not contain clinical notes or laboratory and diagnostic results that aid in the confirmation of the outcomes (ie, cardiac enzymes, electrocardiogram, imaging studies, angiography). The greater variability in the CVA group may be because of the use of different ICD-9-CM code groups to define CVA, which would cause a change in the sensitivity and specificity of case ascertainment. Lastly, only hospitalized events were included as outcomes to improve the reliability of detecting a true outcome.

Event rates for MI or CVA in this study are limited by the ability to detect these events through hospitalization. Events that occur outside the hospital setting may not have been counted, such as those resulting in death prior to admission. The mortality rate is not known in our sample. Loss of events because of preadmission deaths or nonhospitalized events could result in an underestimate of event rates for both groups. Although the magnitude and direction of missed events on the outcome is unknown, if undetected MI and CVA were to occur selectively more often in the neovascular AMD group, then this could explain some of the difference. Finally, the reliability of event rates in this study is supported by their similarity to those in the Cardiovascular Health Study (CHS). The CHS evaluated 5288 participants 65 years or older and reported the incidence of MI and CVA at 13.7 per 1000 PY and 11.5 per 1000 PY, respectively. The incidence rates in our study were similar to that of the CHS at 11.3 MIs per 1000 PY and 9.7 CVAs per 1000 PY.27 Few studies have been conducted in a large sample of subjects with a diagnosis of neovascular AMD describing and comparing the rates of cardiovascular outcomes. Two recent studies on the association of neovascular AMD to MI or CVA outcomes have yielded mixed results. In the current study, the risk of hospitalized MI and CVA was found to be inversely associated with the diagnosis of neovascular AMD. The relationship between neovascular AMD and cardiovascular disease remains unclear and warrants further study.