Occurrence of Secondary Ischemic Events Among Persons With Atherosclerotic Vascular Disease

Barbara G. Vickrey, MD, MPH; Thomas S. Rector, PharmD, PhD; Steven L. Wickstrom, MS; Peter M. Guzy, MD; Elizabeth M. Sloss, PhD; Philip B. Gorelick, MD, MPH; Steven Garber, PhD; Daniel F. McCaffrey, PhD; Michael D. Dake, MD; Regina A. Levin, MPH

Background and Purpose—Few data exist for large managed care populations on the occurrence of subsequent acute ischemic events in persons with established atherosclerotic vascular disease. We estimated the occurrence of secondary stroke, acute myocardial infarction (AMI), and vascular deaths among 2 large, managed care samples.

Methods—With the use of International Classification of Diseases, Ninth Revision, Clinical Modification codes, patients aged ≥40 years and with stroke, AMI, or peripheral arterial disease (PAD) were identified from administrative data of UnitedHealthcare plans during 1995–1998. Stroke, AMI, and PAD cohorts were identified within a commercial insurance sample and a Medicare sample. Cumulative occurrences of subsequent stroke, AMI, or vascular death were estimated by survival analysis.

Results—In the stroke commercial cohort (n=1631; mean age, 62.1 years), cumulative occurrence of subsequent events was 4.2%, 6.5%, 9.8%, and 11.8% at 0.5, 1, 2, and 3 years, respectively; cumulative secondary event occurrence in the AMI commercial cohort (n=6458; mean age, 56.0 years) was 3.5%, 4.8%, 7.3%, and 8.5% and in the PAD commercial cohort (n=5813; mean age, 59.2 years) was 1.5%, 2.8%, 4.8%, and 6.5%, respectively. Cumulative secondary event occurrences were even higher in stroke (n=1518; mean age, 79.5 years), AMI (n=2197; mean age, 76.2 years), and PAD (n=5033; mean age, 76.6 years) cohorts of the Medicare sample: 18.1%, 17.0%, and 8.7%, respectively, at 3 years. More than 75% of each stroke cohort’s secondary events were strokes; more than 75% of each AMI cohort’s secondary events were AMIs. Of the PAD cohorts’ secondary events, 27% to 39% were strokes, 48% to 57% were AMIs, and 13% to 16% were vascular deaths.

Conclusions—Among these managed care enrollees with existing atherosclerotic vascular disease, subsequent ischemic events represent a significant symptomatic disease burden. Given these findings, it is very important to determine whether secondary prevention strategies are being effectively used to manage patients with diagnosed atherosclerosis. (Stroke. 2002;33:901-906.)

Key Words: data interpretation, statistical ■ epidemiology ■ myocardial infarction ■ stroke

People with symptomatic atherosclerotic vascular disease are at increased risk of subsequent ischemic events including acute myocardial infarction (AMI), ischemic stroke, and other vascular events.1–4 Recently developed surgical therapies, devices, and pharmacologic treatments (eg, medications that inhibit platelet aggregation) have the potential to reduce the occurrence of these secondary ischemic events.3

Current estimates of the occurrence of subsequent acute ischemic events among managed care populations in the United States are not generally available and would be useful in estimating the impact of secondary prevention. This study used claims data from several large, managed care organizations from the mid to late 1990s to estimate the cumulative occurrence of secondary ischemic events within samples of employer-based (commercial) and Medicare insurance enrollees identified as having atherosclerotic disease.

Subjects and Methods

Identification of Cohorts With Atherosclerotic Disease
Cohorts of members with atherosclerotic disease were identified by administrative data from commercial and Medicare managed care plans affiliated with UnitedHealthcare. The sample with commercial insurance was drawn from enrollees in managed care organizations in 10 states: Georgia, Michigan, Minnesota, Missouri, Nebraska, North Carolina, Ohio, Rhode Island, South Carolina, and Utah. The Medicare sample was identified from enrollees in Medicare+Choice plans in 4 states: Georgia, Minnesota, Ohio, and Rhode Island.

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Stroke is available at http://www.strokeaha.org
Members with atherosclerotic disease were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes on claims for medical care received over a period from January 1995 through December 1998. Cohorts were selected on the basis of the first indication of an ischemic stroke, AMI, or peripheral arterial disease (PAD). In the commercial sample, only members aged ≥40 years were included to reduce the likelihood of including members with events not due to atherosclerotic vascular disease. Only members aged ≥65 years were included in the Medicare sample. We designed algorithms for administrative data to select members with atherosclerotic events as similar as possible to enrollees in a trial of clopidogrel versus aspirin in patients at risk of secondary ischemic events (ie, the CAPRIE trial). This clinical trial enrolled patients with ischemic stroke, AMI, and PAD. These algorithms were based on the consensus of clinical experts involved as coinvestigators in this study and a review of the literature on validity of ICD-9-CM coding for these conditions.

The ICD-9-CM codes 434 (primary or secondary diagnosis of occlusion of cerebral arteries) and 436 (acute but ill-defined cerebrovascular disease) have been shown to be highly predictive for ischemic strokes. Therefore, we included in the ischemic stroke cohort members hospitalized with a primary or secondary ICD-9-CM code diagnosis of 434.xx or 436. To select this sample, we applied a minimum length-of-stay criterion of 1 day. Because having a carotid endarterectomy significantly changes the prognosis for a secondary event, individuals with a code for carotid endarterectomy during the same hospital stay or within 4 months of discharge were excluded. In addition, the CAPRIE trial did not include individuals who were candidates for anticoagulation, such as those having cardioembolic strokes. Thus, we excluded members who had ≥1 prescription claim for warfarin or ≥2 claims on different days for a prothrombin time laboratory test within 4 months of discharge.

Members with AMI were identified from hospitalizations with a primary diagnosis of AMI (ICD-9-CM code=410.xx) and with a length of stay of ≥2 days. The purpose of applying a minimum length of stay was to exclude brief admissions for possible AMI in the Medicare sample. We designed algorithms for administrative data to select members with atherosclerotic events as similar as possible to enrollees in a trial of clopidogrel versus aspirin in patients at risk of secondary ischemic events (ie, the CAPRIE trial). This clinical trial enrolled patients with ischemic stroke, AMI, and PAD. These algorithms were based on the consensus of clinical experts involved as coinvestigators in this study and a review of the literature on validity of ICD-9-CM coding for these conditions.

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Members with AMI were identified from hospitalizations with a primary diagnosis of AMI (ICD-9-CM code=410.xx) and with a length of stay of ≥2 days. The purpose of applying a minimum length of stay was to exclude brief admissions for possible AMI in the Medicare sample. We designed algorithms for administrative data to select members with atherosclerotic events as similar as possible to enrollees in a trial of clopidogrel versus aspirin in patients at risk of secondary ischemic events (ie, the CAPRIE trial). This clinical trial enrolled patients with ischemic stroke, AMI, and PAD. These algorithms were based on the consensus of clinical experts involved as coinvestigators in this study and a review of the literature on validity of ICD-9-CM coding for these conditions.

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TABLE 1. Characteristics of Persons in Stroke, AMI, and PAD Cohorts and All Cohorts for Medicare and Commercial Samples

<table>
<thead>
<tr>
<th>Type of Secondary Event</th>
<th>No. of persons</th>
<th>Medicare</th>
<th>Commercial</th>
<th>Medicare</th>
<th>Commercial</th>
<th>Medicare</th>
<th>Commercial</th>
<th>Medicare</th>
<th>Commercial</th>
<th>Medicare</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Secondary Events Occurring in</td>
<td>Stroke Cohorts</td>
<td>AMI Cohorts</td>
<td>PAD Cohorts</td>
<td>All Cohorts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>89 (76.7%)</td>
<td>86 (78.9%)</td>
<td>38 (17.9%)</td>
<td>48 (13.6%)</td>
<td>93 (39.1%)</td>
<td>54 (26.6%)</td>
<td>220 (38.9%)</td>
<td>188 (28.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>82 (70.7%)</td>
<td>81 (74.3%)</td>
<td>35 (16.5%)</td>
<td>41 (11.6%)</td>
<td>76 (31.9%)</td>
<td>48 (23.7%)</td>
<td>193 (34.1%)</td>
<td>170 (25.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>7 (6.0%)</td>
<td>5 (4.6%)</td>
<td>3 (1.4%)</td>
<td>7 (2.0%)</td>
<td>17 (7.1%)</td>
<td>6 (3.0%)</td>
<td>27 (4.8%)</td>
<td>18 (2.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>Total</td>
<td>24 (20.7%)</td>
<td>22 (20.2%)</td>
<td>162 (76.4%)</td>
<td>296 (83.9%)</td>
<td>115 (48.3%)</td>
<td>116 (57.1%)</td>
<td>301 (53.2%)</td>
<td>434 (65.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>22 (19.0%)</td>
<td>22 (20.2%)</td>
<td>149 (70.3%)</td>
<td>286 (81.0%)</td>
<td>97 (40.8%)</td>
<td>106 (52.2%)</td>
<td>268 (47.3%)</td>
<td>414 (62.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>2 (1.7%)</td>
<td>0</td>
<td>13 (6.1%)</td>
<td>10 (2.8%)</td>
<td>18 (7.6%)</td>
<td>10 (4.9%)</td>
<td>33 (5.8%)</td>
<td>20 (3.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3 (2.6%)</td>
<td>1 (0.9%)</td>
<td>12 (5.7%)</td>
<td>9 (2.5%)</td>
<td>30 (12.6%)</td>
<td>33 (16.3%)</td>
<td>45 (8.0%)</td>
<td>43 (6.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses represent the percentage of all secondary events occurring in the cohort (ie, the column percent).

The stroke cohort, 6458 in the AMI cohort, and 5813 in the PAD cohort, while the Medicare sample included 1518 in the stroke cohort, 2197 in the AMI cohort, and 5033 in the PAD cohort (Table 1).

The average observation period across all atherosclerotic disease cohorts was approximately 1.3 years in the commercial sample and 1.2 years in the Medicare sample. Relative to the AMI cohorts, higher percentages of the stroke and PAD cohorts were female. Stroke patients in both the Medicare and commercial samples were older on average than corresponding patients in the AMI and PAD cohorts. Hypertension was coded frequently on concurrent or recent claims for all cohorts, ranging from 21% to 31% across these cohorts. Transient ischemic attack was recorded as a diagnosis in a recent claim for 21% to 31% across these cohorts. Transient ischemic attack was recorded as a diagnosis in a recent claim for >20% of each stroke cohort and was rare in the other cohorts.

Cumulative Occurrence of Secondary Events by Cohort Within the Medicare and Commercial Samples

Across the 3 atherosclerotic vascular disease cohorts combined, 566 in the Medicare sample and 665 in the commercial sample experienced a secondary event (stroke, AMI, or vascular death) at some time during the observation period (Table 2). More than 75% of the secondary events were strokes in the stroke cohorts and were AMIs in the AMI cohorts (Table 2). A higher percentage of secondary events occurring in the PAD cohorts were fatal events (ie, other vascular deaths and fatal stroke and AMI) than of secondary events occurring in the AMI and stroke cohorts (Table 2).

The Figure shows cumulative occurrence data for each atherosclerotic disease cohort of the Medicare and commercial samples. In the stroke cohort of the commercial sample, cumulative occurrence of subsequent events was 4.2%, 6.5%, 9.8%, and 11.8% at 0.5, 1, 2, and 3 years, respectively. Cumulative occurrence of secondary events in the AMI cohort of the commercial sample was 3.5%, 4.8%, 7.3%, and 8.5% and in the PAD cohort of the commercial sample was 1.5%, 2.8%, 4.8%, and 6.5% at 0.5, 1, 2, and 3 years, respectively. In the Medicare sample, secondary event occurrences at 0.5, 1, 2, and 3 years were 4.3%, 7.7%, 14.1%, and 18.1% in the stroke cohort; 6.0%, 8.8%, 13.9%, and 17.0% in the AMI cohort; and 2.3%, 3.7%, 6.6%, and 8.7% in the PAD cohort, respectively. Overall cumulative occurrences were higher in the AMI and PAD cohorts of the Medicare sample.
than in analogous cohorts of the commercial sample ($P<0.001$ in both cases), with a trend toward higher overall cumulative occurrences for the stroke cohort of the Medicare sample than for the stroke cohort of the commercial sample ($P=0.06$). The cumulative occurrences of each of the 3 types of secondary ischemic events (AMI, stroke, and other vascular disease) at 0.5, 1, 2, and 3 years, by atherosclerotic disease cohort, are shown in Tables 3 and 4 for commercial and Medicare samples, respectively.

**Discussion**

This study found a substantial occurrence of subsequent ischemic events among members of commercial and Medicare managed care plans that were identified by claims whose ICD-9-CM codes were consistent with atherosclerotic disease. Within the Medicare and commercial samples, the stroke cohorts were the oldest and the AMI cohorts were the youngest and were predominantly male. As expected given the older age of the Medicare sample in our study, the cumulative incidence of secondary events was higher in the Medicare sample’s atherosclerotic disease cohorts than in the commercial sample’s analogous cohorts. These findings are consistent with the findings of past epidemiological studies.

We also found that $>75\%$ of secondary events in the stroke cohort were strokes; analogously, AMI accounted for $>75\%$ of secondary events in the AMI cohort. Thus, a large majority of subsequent ischemic events in each of these cohorts is the same type as that of the preceding event. Such data should aid in targeting risk reduction and patient education efforts regarding subsequent events. The results of this study also show that while the PAD cohort we identified had the lowest cumulative occurrence of secondary events compared with the stroke and AMI cohorts, the PAD cohort experienced the highest case fatality or proportion of secondary events that were fatal stroke, fatal AMI, and other vascular deaths. This finding should heighten attention focused on determining the reasons for the higher proportion of fatal secondary events among those with PAD who have a secondary event, to guide future preventive efforts.

In contrast to this study, previously published studies of rates of subsequent atherosclerotic events have tended to focus on 1 atherosclerotic disease cohort and/or 1 subsequent event type. Cumulative occurrence of a subsequent atherosclerotic event (stroke, AMI, or vascular death) by type of initial atherosclerotic disease diagnosis and whether a person had Medicare or commercial insurance. AMICOM indicates AMI/commercial insurance cohort (n=6458); PADCOM, PAD/commercial insurance cohort (n=5813); STRCOM, stroke/commercial insurance cohort (n=1631); AMIMCR, AMI/Medicare insurance cohort (n=2197); PADMCR, PAD/Medicare insurance cohort (n=5033); and STRMCR, stroke/Medicare insurance cohort (n=1518).

**TABLE 3. Cumulative Occurrence* of Secondary Events in Commercial Sample by Cohort and Type of Secondary Event**

<table>
<thead>
<tr>
<th>Time Since Initially Identified Event, y</th>
<th>Stroke Cohort (n=1631)</th>
<th>AMI Cohort (n=6458)</th>
<th>PAD Cohort (n=5813)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMI</td>
<td>Stroke</td>
<td>OVD</td>
</tr>
<tr>
<td>0.5</td>
<td>(n=22)</td>
<td>(n=86)</td>
<td>(n=1)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.68%</td>
<td>3.55%</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>1.26%</td>
<td>5.31%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>2.25%</td>
<td>7.57%</td>
<td>0.14%</td>
</tr>
<tr>
<td>3</td>
<td>3.03%</td>
<td>8.88%</td>
<td>0.14%</td>
</tr>
</tbody>
</table>

OVD indicates other vascular death.

*Percentages of each cohort that had experienced each type of secondary event at 0.5, 1, 2, and 3 years after an individual’s initially identified event were determined from Kaplan-Meier survival analysis.

†The category of secondary AMI includes fatal and nonfatal AMIs. The category of secondary stroke includes fatal and nonfatal strokes.
In conclusion, this analysis shows that among persons with managed care organization might be able to identify for disease management programs.

A second limitation is that in contrast to stroke and AMI, there are scarce published data on the utility of ICD-9-CM codes for identifying PAD. It is likely that the PAD cohorts we identified included some individuals without PAD or who would not meet more specific clinical criteria. It is possible that the diagnosis codes used might have included, particularly in an outpatient setting, individuals with potential or suspected PAD but who had not undergone confirmatory testing. It is not possible to assess the outcome of diagnostic testing from these administrative claims data. Given that the algorithm might overestimate the “denominator” of the occurrence estimates for PAD, the estimates reported herein probably reflect lower bound estimates of the occurrence of secondary events among individuals with PAD.

Because administrative databases are likely to have some coding errors and do not contain extensive clinical information, some members and secondary events may have been misclassified. In addition, the algorithms used could have missed some ischemic events. For example, a member with a primary diagnosis of cardiac arrest and a secondary diagnosis of AMI may have had a cardiac arrest induced by AMI, but that would not be identified by the protocol used in this study. To address this issue, we used diagnostic codes for AMI and stroke that have high positive predictive values,6–11,17–19 and we reviewed more detailed facility and provider claims in judging the inclusion of potential vascular deaths.

Finally, the cumulative occurrence estimates reported here may not apply to other practice settings and locations. The demographic and clinical characteristics of the members of these plans, as well as care patterns, may differ from those in other plans or areas in the United States not included in our study. We note, however, that commercial plans represented here are from 10 states in 4 regions of the United States, and Medicare managed care plans from which that sample was drawn are from 4 states in 3 regions of the United States.

In conclusion, this analysis shows that among persons with atherosclerotic vascular disease enrolled in several managed care plans in the mid to late 1990s, the occurrence of subsequent ischemic events is substantial. In light of thera-

### Table 4. Cumulative Occurrence* of Secondary Events in Medicare Sample by Cohort and Type of Secondary Event

<table>
<thead>
<tr>
<th>Time Since Initially Identified Event, y</th>
<th>Stroke Cohort (n=1518)</th>
<th>AMI Cohort (n=2197)</th>
<th>PAD Cohort (n=5033)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMI (n=24)</td>
<td>Stroke (n=89)</td>
<td>OVD (n=3)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.65%</td>
<td>3.62%</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>1.56%</td>
<td>6.23%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>3.39%</td>
<td>10.77%</td>
<td>0.30%</td>
</tr>
<tr>
<td>3</td>
<td>5.05%</td>
<td>12.17%</td>
<td>1.81%</td>
</tr>
</tbody>
</table>

OVD indicates other vascular death.

*Percentages of each atherosclerotic disease cohort that had experienced each type of secondary event at 0.5, 1, 2, and 3 years after an individual’s initially identified event were determined from Kaplan-Meier survival analysis.

†The category of secondary AMI includes fatal and nonfatal AMIs. The category of secondary stroke includes fatal and nonfatal strokes.

The CAPRIE trial included all 3 of our study cohorts and assessed the same study outcome variables of ischemic stroke, AMI, and vascular death; the mean duration of follow-up was 1.9 years. The total secondary event rate per year in the stroke cohort was between 7% and 8%; the event rate per year in the AMI cohort was 4.8% to 5.0%; and the event rate per year in the PAD cohort ranged from 3.7% to 4.9%. The mean age of the CAPRIE study cohort was 62.5 years. While direct comparisons must take into account the different study periods, the event rates reported herein are slightly higher than the occurrence rates reported herein.

There are several limitations of this study. We note that this study may include individuals with third and later events and is not limited to patients with second events. This is because some initial events would have preceded the observation period of our analysis. Thus, this study is not strictly an analysis of the incidence of second events after an initial event within a cohort with established atherosclerotic vascular disease, but it represents an analysis of subsequent events after an event first identified within an administrative database of health plan members over a specific time frame. However, the present study represents those members a
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References
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