Occurrence of Secondary Ischemic Events Among Persons With Atherosclerotic Vascular Disease

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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. 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.

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.

Received October 1, 2001; final revision received December 12, 2001; accepted December 17, 2001.
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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.5 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.6–9 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 which an AMI was “ruled out.” The ICD-9-CM code of 410 has previously been found to be highly predictive of a clinically validated AMI among hospitalized patients.10,11 To identify a PAD sample, members who had a hospital admission or a physician office visit with a primary or secondary diagnosis of atherosclerosis of native arteries of the extremities (ICD-9-CM code=440.2x) or atherosclerosis of bypass grafts of the extremities (ICD-9-CM code=440.3x) were included. Because existing published literature on the predictive validity of ICD-9-CM codes for PAD was scant, we based this selection on input from coinvestigators with clinical expertise in vascular disease.

### Identification of Subgroups With a Secondary Ischemic Event

**Nonfatal and Fatal Stroke and AMI**

Secondary ischemic events were defined as the first occurrence (within the cohorts identified as having atherosclerotic disease) of a stroke or AMI during the observation period. Secondary events were identified by an emergency department visit with a discharge status of death or by a hospitalization. Codes used to identify a stroke or AMI had to be listed as the primary diagnosis for the emergency department visit or the hospitalization. The diagnosis codes were 434 or 436 (for stroke) and 410 following peripheral vascular operations, procedures, infections, or amputations.

**Other Vascular Death**

The criteria we used to define an “other vascular death” were evidence from the administrative database for fatal events due to pulmonary embolism; congestive heart failure attributable to cardiovascular disease; visceral or limb infarction due to peripheral vascular disease; vascular operation, procedure, or amputation related to atherosclerosis; or another diagnosis strongly indicating an atherosclerotic disease vascular event as the potential cause of death.

Within the study samples (with the exclusion of patients identified as having a secondary stroke or AMI as described above), patients with a hospital or emergency department facility claim with a discharge status code of “death” were identified. Among these, patients with primary discharge codes unrelated to a potential vascular death were excluded, leaving 308 patients identified as possibly eligible for categorization as “other vascular death.” For these patients, all facility and provider claims for the hospital admission or emergency department visit associated with the discharge code of death were reviewed by a cardiologist and a neurologist. Each patient was categorized as either a definite or possible vascular death or not a vascular death on the basis of diagnoses and procedures listed on claims. The disposition of each possible vascular death was determined by a stroke neurologist with expertise in vascular death identification for clinical trials. To validate the discharge status of death, we conducted an administrative database review, looking for evidence of claim activity after the indicated date of death. If claims were found with dates of service after the date of death, these cases were excluded from the other vascular death category.

With the use of these procedures, a total of 88 of 308 patients were judged to meet the criteria for “other vascular death.” The types of other vascular deaths identified among these 88 patients were 1 related to pulmonary embolism, 11 related to congestive heart failure, 9 related to cardiovascular procedures, 9 indicating cardiac arrest in the presence of a cardiac condition, 6 with other acute cardiac events, 9 with aortic aneurysm, 2 following carotid endarterectomy, and 41 following peripheral vascular operations, procedures, infections, or amputations.

### Statistical Analysis

Within each sample, duration of observation, sex, and age were determined overall and for each atherosclerotic disease cohort. While the actual prevalence of comorbidities of hypertension, diabetes, and transient ischemic attack cannot be determined from claims data, we constructed a proxy measurement of their prevalence by assessing the proportion of each cohort having 1 of these diagnoses coded on a claim either at the time of or during the 3 months preceding the qualifying event.

Cumulative occurrences of subsequent events (stroke, AMI, and other vascular death) were estimated for each cohort (stroke, AMI, and PAD) of the commercial and Medicare samples by Kaplan-Meier survival analysis.12 The significance of differences between the survival curves was assessed by the log-rank statistic. For each of the atherosclerotic disease cohorts in the commercial and Medicare samples, the percentages of each type of secondary event (AMI, stroke, or other vascular death) by 0.5, 1, 2, and 3 years after the initially identified event were also calculated.

This study was approved by the RAND Institutional Review Board, and procedures for data privacy met guidelines of both RAND and the Center for Health Care Policy and Evaluation of UnitedHealth Group.

### Results

**Characteristics of Stroke, AMI, and PAD Cohorts**

Of the 23 490 members who met study inclusion criteria, 840 either died or disenrolled during their index atherosclerotic event hospitalization or were still hospitalized with their index atherosclerotic event at the end of the study observation period (December 31, 1998). After these members were excluded, the commercial sample included 1631 members in...
TABLE 1. Characteristics of Persons in Stroke, AMI, and PAD Cohorts and All Cohorts for Medicare and Commercial Samples

<table>
<thead>
<tr>
<th></th>
<th>Stroke Cohorts</th>
<th>AMI Cohorts</th>
<th>PAD Cohorts</th>
<th>All Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medicare</td>
<td>Commercial</td>
<td>Medicare</td>
<td>Commercial</td>
</tr>
<tr>
<td>No. of persons</td>
<td>1518</td>
<td>1631</td>
<td>2197</td>
<td>6458</td>
</tr>
<tr>
<td>Days of observation, mean</td>
<td>363</td>
<td>420</td>
<td>432</td>
<td>483</td>
</tr>
<tr>
<td>% Female</td>
<td>61.4</td>
<td>46.4</td>
<td>49.7</td>
<td>23.4</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>79.5 (7.8)</td>
<td>62.1 (12.6)</td>
<td>76.2 (7.2)</td>
<td>56.0 (9.6)</td>
</tr>
<tr>
<td>Recent claims diagnosis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) with diabetes</td>
<td>406</td>
<td>497 (30.5%)</td>
<td>618</td>
<td>1380 (21.4%)</td>
</tr>
<tr>
<td>No. (%) with hypertension</td>
<td>1078</td>
<td>1118 (68.6%)</td>
<td>1412 (64.3%)</td>
<td>3172 (49.1%)</td>
</tr>
<tr>
<td>No. (%) with TIA</td>
<td>318</td>
<td>409 (25.1%)</td>
<td>47 (2.1%)</td>
<td>53 (0.8%)</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.
*The percentage of each cohort having one of these diagnoses recorded as a diagnostic code on a claim either at the time of or during the 3 months preceding their initial event.

The stroke cohort, 6458 in the AMI cohort, and 5813 in the PAD cohort, were female. Stroke patients in both the Medicare and commercial samples were older than corresponding patients in the AMI and PAD cohorts. Hypertension was coded frequently on concurrent or recent claims for all cohorts, ranging from a low of 37% of the PAD cohort of the commercial sample to a high of 71% of the stroke cohort of the Medicare sample. Comparable estimates for diabetes ranged from 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.

TABLE 2. Type of Secondary Events in Stroke, AMI, PAD, and All Cohorts for Medicare and Commercial Samples

<table>
<thead>
<tr>
<th>Type of Secondary Event</th>
<th>Stroke Cohorts</th>
<th>AMI Cohorts</th>
<th>PAD Cohorts</th>
<th>All Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medicare (n=116)</td>
<td>Commercial (n=109)</td>
<td>Medicare (n=212)</td>
<td>Commercial (n=353)</td>
</tr>
<tr>
<td>Stroke</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>
</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>
</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>
</tr>
<tr>
<td>AMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24 (20.7%)</td>
<td>22 (20.2%)</td>
<td>162 (76.4%)</td>
<td>296 (83.9%)</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>
</tr>
<tr>
<td>Fatal</td>
<td>2 (1.7%)</td>
<td>0</td>
<td>13 (6.1%)</td>
<td>10 (2.8%)</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>
</tr>
</tbody>
</table>

Values in parentheses represent the percentage of all secondary events occurring in the cohort (ie, the column percent).
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. These studies have shown that the majority of secondary events are of the same type as the preceding event. Our findings are consistent with these previous studies, and we have extended this observation to a broader range of atherosclerotic events and insurance types.

We also found that the proportion of secondary events that were fatal was higher in the PAD cohort compared with the stroke and AMI cohorts. This finding is consistent with previous studies that have shown that PAD is associated with an increased risk of mortality. Further research is needed to determine the underlying reasons for this higher mortality rate.

The results of this study have implications for clinical practice and public health policy. First, clinicians should be aware of the substantial occurrence of subsequent ischemic events among members of commercial and Medicare managed care plans. This knowledge can inform risk stratification and patient education efforts. Second, these findings highlight the importance of targeting interventions to prevent secondary events, particularly among the PAD cohort. Finally, these results underscore the need for future research to better understand the reasons for the higher proportion of fatal secondary events among those with PAD who have a secondary event.
event. In addition, many previous analyses examined cohorts selected for clinical trials. One study of factors predicting recurrent AMI after an initial AMI reported 1-year reinfarction rates of 6.9% for men and 5.6% for women in a sample of survivors of a hospitalization for a first AMI in Israel in the early 1980s. A second study of sex-related differences in factors predicting recurrent AMI found 26-month reinfarction rates of 8.5% in men and 5.5% in women. A clinical trial of the impact of an 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor on stroke occurrence in subjects (mean age, 59 years) with an AMI showed an approximately 0.6% 1-year stroke incidence in the placebo arm, which is similar to the 1-year stroke occurrence in the commercial AMI sample in the managed care plans we studied. The Edinburgh Artery Study, a population-based epidemiological study of PAD that began in the late 1980s, found that the 5-year incidence of AMI in subjects with intermittent claudication was 8.2% and the 5-year incidence of stroke or transient ischemic attack was 6.8%.

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 differences in study designs, these rates appear similar to or 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 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, 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-
neutic advances demonstrated to be effective for secondary prevention, future research should include assessment of care patterns for secondary prevention in these high-risk patients, with the goal of determining whether there are gaps between actual care and evidence-based recommendations for high-quality care that can be bridged through quality improvement programs.

Acknowledgments
Bristol-Myers-Squibb/Sanofi Pharmaceuticals Partnership provided funding to RAND for this study. The topic of the study was agreed upon with the funding organization at the outset of the project, but RAND retained full rights to design, analyze, interpret, and publish results as judged appropriate by the research team. All authors were funded through RAND either as employees, subcontractors, or consultants. Dr. Gorelick was a consultant to RAND on the project and is on the Speakers Bureau of Bristol-Myers-Squibb. No other authors have potential conflicts of interest related to the subject of the manuscript. We thank Margaret J. Burgess for technical assistance in conducting the SAS programming for the data analyses.

References
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Stroke. 2002;33:901-906
doi: 10.1161/hs0402.105246

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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