Use of Oral Antithrombotic Agents Among Health Maintenance Organization Members With Atherosclerotic Cardiovascular Disease

Jonathan B. Brown, MPP, PhD; Thomas E. Delea, MSIA; Gregory A. Nichols, PhD; John Edelsberg, MD, MPH; Patricia J. Elmer, PhD, MS; Gerry Oster, PhD

Background: Numerous randomized trials document the value of antithrombotic agents for the treatment of cardiovascular disease (CVD). Although antithrombotic agents are often prescribed at hospital discharge after CVD-related events, much less is known about the ongoing use of such agents.

Methods: We examined the use of oral antithrombotic agents among a random sample of 2500 persons with atherosclerotic CVD who were enrolled in Kaiser Permanente Northwest Region, a not-for-profit group-model health maintenance organization. Study subjects were identified based on a diagnosis of coronary heart disease, ischemic stroke or transient ischemic attack, or peripheral arterial disease in outpatient problem lists, visit records, and hospital discharge abstracts. Use of prescription antithrombotic agents was identified from pharmacy dispensing records. Regular use of aspirin, recall of aspirin advice and education, and other patient characteristics were ascertained by mail survey.

Results: Among the 1844 subjects who returned the survey and answered the question regarding aspirin use, 84% were using either aspirin (72%) or a prescription antithrombotic agent (12%), typically warfarin sodium. Antithrombotic therapy was relatively underused in persons with peripheral arterial disease (75% used an antithrombotic agent and 62% used aspirin). Use of antithrombotic agents, including aspirin, did not differ by age but was higher among men (87%, 76%) than women (81%, 67%). Nearly all subjects reported having received aspirin education (94%) or advice (81%); recall of education or advice was associated with a dramatically higher likelihood of using antithrombotic agents. To a lesser extent, so was contact with a cardiologist or vascular surgeon during the prior year.

Conclusions: High rates of use of antithrombotic agents can be achieved among persons with CVD in integrated not-for-profit health systems with mechanisms in place to encourage such use, including guidelines, messages to clinicians, nurse care management, alerts and routines embedded in electronic medical records, and direct mailings to patients. Continued efforts should be made in all settings to optimize the use of antithrombotic therapy among persons at an elevated risk of atherothrombotic events.

Arch Intern Med. 2002;162:193-199

Numerous randomized controlled trials demonstrate the value of oral antithrombotic therapy in preventing myocardial infarction (MI), ischemic stroke, and vascular death in patients with clinical atherosclerotic cardiovascular disease (CVD). Two types of oral antithrombotic agents are available—antiplatelet agents and anticoagulants. Aspirin is the most extensively studied and by far the most frequently used antiplatelet agent. Regular use of low-dose aspirin for the secondary prevention of atherothrombotic events in patients with established CVD is widely recommended. In addition to aspirin, 3 other oral antiplatelet agents—clopidogrel bisulfate, ticlopidine hydrochloride, and dipyridamole—and 1 oral anticoagulant—warfarin sodium—are used in the United States. While studies consistently report that most patients with acute MI receive orders for aspirin on hospital discharge, data on the long-term use of antithrombotic agents among outpatients with CVD are limited and inconsistent. In the Atherosclerosis Risk in Communities Study, only 53% of middle-aged subjects with a self-reported history of MI, and 37% of those with a self-reported history of stroke, took aspirin. More recently, Cook et al found that only 43% of respondents to the 1996 National Family Opinion Mail Panel survey with a self-reported history of CVD reported taking aspirin regularly. Similarly, using data from the 1996 National Ambulatory Medical Care Survey, Stafford found that only 34% of physicians’ office visits for coronary heart disease (CHD) included a
PARTICIPANTS AND METHODS

RESEARCH SETTING

Kaiser Permanente Northwest provides comprehensive prepaid coverage to about 430,000 persons, or approximately 20% of the population of metropolitan Portland. Plan members are similar in age, sex, ethnicity, and economic status to the area population as a whole.11 Kaiser Permanente Northwest maintains administrative and clinical electronic end-user (searchable) databases containing information on member demographics; inpatient admissions; pharmaceutical prescriptions; sales of prescription drugs from Kaiser Permanente pharmacies; outpatient contacts, including visits, diagnoses, problem lists (patient-specific cumulative lists of diagnoses), outside claims, and referrals; laboratory tests; and measurements, such as weight and blood pressure. During this study, however, aspirin use could not be documented from these sources.

POPULATION AND SAMPLE

To identify all KPNW members diagnosed as having atherosclerotic CVD as of March 31, 1999, we searched all outpatient problem lists for the prior 3-year period, and all inpatient discharge abstracts for the prior 13-year period, for diagnoses of CHD (International Classification of Diseases, Ninth Revision, Clinical Modification codes 410.xx, 411.0, 411.1, 411.8x, 412, 413.xx, 414.0x, 36.0x, and 36.1x), ischemic stroke or transient ischemic attack (TIA) (International Classification of Diseases, Ninth Revision, Clinical Modification codes 433.xx, 434.xx, and 435.x), and peripheral arterial disease (PAD) (International Classification of Diseases, Ninth Revision, Clinical Modification codes 440.2x and 443.9). Excluding members who died or left the health plan before March 31, 1999, a total of 19,502 persons met the selection criteria. After ascertaining that a simple random sample of 2500 persons with CVD would capture 200 persons with PAD, our smallest subgroup of interest, we used SAS statistical software (SAS Institute Inc, Cary, NC) to select such a sample from a file containing the entire eligible population.

QUESTIONNAIRE

We developed a 5-page questionnaire that included questions about regular aspirin use, adverse effects, and reasons for not using aspirin. We ascertained aspirin use based on an affirmative response to the question: “Do you take aspirin or an aspirin-containing product regularly? (Regularly means at least every other day.)” To assist respondents in answering this question accurately, the question was followed with a list of aspirin and aspirin-containing products and a list of products that do not contain aspirin (eg, acetaminophen [Tylenol] and ibuprofen [Motrin]). We also asked members whether they had received education about aspirin (“Has a doctor or other health professional ever told you that taking aspirin or an aspirin-containing product could help prevent heart attack or stroke?”) or advice to use it (“Has a doctor or other health professional prescribed or suggested that you take aspirin or an aspirin-containing product regularly?”). The questionnaire also included the Medical Outcomes Study 12-Item Short-Form Health Survey, supplemented with all 10 items from the Physical Function scale of the Medical Outcomes Study 36-Item Short-Form Health Survey.13,14 We also asked members about self-care, smoking status, educational level, race or ethnicity, and household income. Finally, we asked members about any adverse effects of aspirin that they had experienced. A copy of the questionnaire may be obtained at http://www.kpchr.org/info/present/antiplatelet-brown.pdf.

Cover letters, questionnaires, and prepaid return-mailing envelopes were sent via US Post Office Priority Mail to all study subjects during May 1999. A second complete priority mailing was sent during June 1999 to all those who did not respond to the first mailing.

ADMINISTRATIVE DATA

We ascertained the age and sex of all study subjects from HMO enrollment records. We identified persons who had received prescription antithrombotic agents (clopidogrel, dipyridamole, ticlopidine, or warfarin) using electronic pharmacy dispensing records. We labeled subjects as users of prescription antithrombolytic therapy if they purchased any of these agents during the 3 months preceding the initial mailing of the survey. To determine whether patients had other comorbid conditions known to be associated with antiplatelet and anticoagulant use (atrial fibrillation, valvular heart disease, or venous thromboembolism) or with increased risk of CVD (diabetes mellitus), we searched inpatient discharge diagnoses and outpatient problem lists and visit diagnoses. Prestudy use of services (prescription drugs and ambulatory visits) was ascertained from administrative databases for the 1-year period spanning July 1, 1998, through June 30, 1999. Prior CVD-related events were identified from hospital discharge summaries.

STATISTICAL ANALYSES

We compared the baseline characteristics of survey respondents with those of nonrespondents using the t test for differences in means and the Pearson χ² test for differences in proportions. We calculated the percentage of patients with a prescription for an antithrombolytic agent in the 3 months before the survey, the percentage reporting regular use of aspirin, and the percentage who were not using an oral antithrombotic agent of any type (ie, no prescription antithrombotic or aspirin use). We calculated the percentage of subjects receiving antithrombotic therapy in subsets defined by demographic characteristics, comorbidities, and medical and self-care characteristics. We also examined the proportion of regular aspirin users who reported experiencing adverse effects of aspirin therapy. All analyses were performed using SAS statistical software, version 6.12.
Other concomitant medical conditions included atrial fibrillation; and 11%, PAD (not mutually exclusively) (sample had a history of CHD; 20%, ischemic stroke or TIA; and 11%, PAD (not mutually exclusively) (sample had a history of CHD; 20%, ischemic stroke or TIA). Subjects who returned the survey and answered the question regarding aspirin use. (Aspirin-item nonrespondents).

Approximately 81% of the subjects in the analysis sample had a history of CHD; 20%, ischemic stroke or TIA; and 11%, PAD (not mutually exclusively) (Table 1). Other concomitant medical conditions included atrial fibrillation (17%), valvular heart disease (10%), and venous thromboembolism (2%). Questionnaire nonrespondents were slightly younger than those in the analysis sample, less likely to have CHD, and more likely to have diabetes or ischemic stroke or TIA. Aspirin-item nonrespondents, on the other hand, were almost 5 years older than the analysis sample (on average), were less likely to be men, and were more likely to have PAD, atrial fibrillation, valvular heart disease, and venous thromboembolism. Use of prescription antithrombotic agents was similar among questionnaire nonrespondents, aspirin-item nonrespondents, and those in the analysis sample, as was the time since the last CVD-related event (approximately 2½ years in all 3 groups).

USE OF ANTITHROMBOTIC AGENTS
BY DEMOGRAPHIC CHARACTERISTICS
AND COMORBIDITIES

Among the 1844 subjects in the analysis sample, 84% were using an oral antithrombotic agent, including 72% who reported taking aspirin regularly and 12% who were receiving a prescription antithrombotic agent (Table 2). Included among those who purchased prescription agents were 70 persons (4% of the analysis sample) who also reported regular use of aspirin. The most commonly used prescription agent was warfarin (9%), followed by clopidogrel (1%), ticlopidine (1%), and dipyridamole (<1%).

Almost one quarter of the subjects with PAD were not using an antithrombotic agent, nearly twice the proportions among those with histories of CHD and ischemic stroke or TIA. Persons with a history of ischemic stroke or TIA were much more likely to be using a prescription agent than those with a history of CHD. Persons with histories of atrial fibrillation, valvular heart disease, and venous thromboembolism also used prescription agents more frequently.

Across age groups, use of antithrombotic agents was similar but not identical. Persons younger than 75 years were more likely to report use of aspirin than those who were older, and those 75 years and older were more likely
to be receiving prescription agents. As a result, the mean age was higher for persons using prescription antiplatelet agents (72.2 years) than for those using aspirin (69.3 years). Women were less likely than men to take aspirin, but only slightly more likely to have purchased a prescription agent. Overall, antithrombotic use was higher among men (87%) than among women (80%).

Members of minority ethnic groups appeared infrequently in the study sample; estimates of their use of antithrombotic agents are, therefore, unreliable. Educational level was not associated with the use of these agents, but household income was, with less use at the highest and lowest levels of annual income (<$10,000 and ≥$100,000).

Many subjects recalled having received education and advice regarding the use of aspirin (Table 3). Among the 1517 subjects who answered the question concerning aspirin education, 84% remembered receiving education. A slightly lower proportion of those who answered the aspirin advice question (81% of 1821) recalled receiving such advice. Recall of patient education and advice regarding aspirin was strongly associated with higher rates of use of antithrombotic agents. More than 80% of those who recalled receiving aspirin education or advice reported that they used aspirin regularly, compared with 12% among those who did not recall receiving aspirin advice and 31% among those who did not recall receiving aspirin education. Among the 342 subjects who did not recall receiving advice, 52% were not using an antithrombotic agent, and those who were using antithrombotic agents were 3 times more likely to be using a prescription agent than aspirin.

Among the 284 subjects who were not using an antithrombotic agent and who answered the question concerning aspirin advice, 62% did not recall ever having received such advice. Of the 108 persons who were not using an antithrombotic agent who did recall being advised to take aspirin, 80% reported at least 1 reason for avoiding the medication (data not shown). The most commonly cited reasons were “taking too many pills” (36%), allergy or side effects (34%), and forgetfulness (29%). One fifth said they “don’t like taking medication or pills,” and a few (5%) said they could not afford the cost.

The use of aspirin vs prescription agents was associated with measures of overall health, physical function, and comorbidity. Of the subjects reporting poor overall health, 26% were receiving prescription agents compared with 3% of those reporting excellent health. The mean Medical Outcomes Study 36-Item Short-Form Health Survey Physical Function scale score was 61.1 among aspirin users vs 47.6 among those using prescription agents, but the Medical Outcomes Study 12-
Item Short-Form Health Survey Mental Health scale scores were similar among the 2 groups.

Contact with a cardiologist or a vascular surgeon during the previous year was associated with greater use of aspirin and prescription antithrombotic agents. A neurologic visit was also associated with greater use of prescription agents (22%), but not of aspirin. Persons using prescription agents had more total pharmacy distributions in the year before the survey (43.8 vs 28.8) and more ambulatory care visits (16.4 vs 12.2). Persons whose most recent hospitalization for CVD occurred 6 or more years before the survey were much less likely to be using an antithrombotic agent than those who were hospitalized for CVD during the preceding year (67% vs 86%).

Approximately 44% of the persons who used aspirin regularly reported 1 or more adverse effects from the medication (data not shown). The most frequently reported adverse effects were bruising (18%), upset stomach/heartburn (17%), ringing in the ears (16%), epistaxis or other bleeding (8%), and asthma or shortness of breath (7%). Reports of black tarry stools (2%), severe allergic reactions (such as rash, hives, and swelling of the tongue) (1%), and other adverse effects (including ulcer) (1%) were rare. The number of persons reporting adverse effect data was 1397.

**COMMENT**

The rate of aspirin use that we observed is substantially higher than the rates reported in the 3 large community-based studies of antithrombotic use among US patients with CVD. However, it is similar to the rate recently reported for members of another integrated not-for-profit HMO. Three factors probably explain these differences and this similarity.

First, the 3 community-based studies may underestimate the use of aspirin among patients with CVD in the United States. The Atherosclerosis Risk in Commu-
Based on a physician survey, Stafford et al. reported rates of aspirin use by trained interviewers, not on a mail survey). The Atherosclerosis Risk in Communities Study also, but this study was based on detailed interviews by trained interviewers, not on a mail survey. Based on a physician survey, Stafford et al. reported rates of aspirin use that were less than half of those observed in our study, which relied on patient self-report. Estimates of the use of prescription antithrombotic agents were virtually the same (11%) in the 2 studies, however. At our study site, while 72% of respondents said that they were taking aspirin prophylaxis, the electronic medical record documented only about 20% (a subsequent campaign by the HMO dramatically improved documentation, to 69%).

Second, we believe that the multiple initiatives to promote aspirin use that were undertaken at KPNW in the 4 years before the survey contributed to the relatively high rates of antithrombotic use that we observed. These included developing a guideline, reinforcing it with letters to physicians, implementing aspirin-aware case management programs, and ensuring aspirin initiation after hospitalization. The effectiveness of one of these initiatives—the effort to ensure that members hospitalized for CVD were discharged with a prescription for aspirin—is suggested by our finding that antithrombotic use was more common among persons whose last CVD-related hospitalization occurred after 1995. More than 90% of KPNW members with CVD recalled receiving aspirin education or advice, and these members were much more likely to use an antithrombotic agent than those who did not.

Last, we believe that the culture, structure, and resources of a large, integrated, not-for-profit HMO may have contributed to the high rates of use seen in our study and in the study by O’Connor et al. at HealthPartners in Minneapolis, Minn. At KPNW and similar institutions, clinicians and patients interact within an organizational structure and culture that focus on population-based preventative care. Primary care and CVD specialists communicate frequently, not only through patient referrals but also via telephone consultations and electronic mail (in addition to hard-copy and intranet-based guidelines and alerts). Use of a single integrated medical record (electronic since 1995 at KPNW) facilitates documentation and communication of medication use history. For example, the previously mentioned increase in aspirin documentation between 1999 and 2000 was achieved by alerts and processes embedded in the electronic medical record, by a groupwide financial incentive, and by leadership from a physician-led management structure.

Whether similar results could be obtained in less integrated clinical settings remains to be seen. Many of the investments made at KPNW could be duplicated in decentralized HMO and fee-for-service settings, including aspirin-aware case management services for persons with diabetes and CVD and programs to ensure that all persons discharged from the hospital with CVD receive aspirin. A simple mailing to clinically appropriate persons identified from hospital and drug dispensing records may increase aspirin use at a nominal cost. The future development of Internet-based and/or “smart card” integrated medical records may help.

Several limitations of our study should be noted. First, we relied on patient self-report to measure aspirin use. In an effort to give the right answer, some respondents may have overestimated the regularity of their use of aspirin (social desirability bias). We attempted to minimize this problem by explicitly defining regularly in the question regarding use of aspirin and by listing aspirin-containing and non-aspirin-containing products. Our cover letter also emphasized that answers would not be shared with clinicians and would not affect respondents’ health plan benefits or medical care. We cannot directly measure social desirability bias, but it is encouraging that only 4% of subjects said they were taking aspirin regularly, yet had purchased a prescription antiplatelet agent during the previous 3 months. Switching among agents and the simultaneous prescription of warfarin and aspirin could account for much or all of this overlap.

A second limitation of any questionnaire-based study is survey and item nonresponse. Persons with a history of ischemic stroke or TIA were significantly less likely to return our survey, as were younger persons and those with diabetes. Some persons who had experienced stroke may have been physically unable to complete and return the survey. In the KPNW membership, younger persons are generally less likely to return health surveys (and less likely to adhere to medical advice). The lower rate of response among persons with diabetes may be related to competition from diabetes’ surveys that were concurrently fielded by other researchers. We found no evidence that persons using prescription antithrombotic agents were less likely to complete the survey or to answer the aspirin use question. The rate of use of prescription agents was 14% among nonrespondents, not significantly different from the 12% rate of use among respondents ($P = .42$). Similarly, the rate of use of prescription agents among the 108 survey respondents who failed to answer the question concerning aspirin use was 15%, again not significantly different from the rates found in other subgroups. Nevertheless, we are unsure whether nonrespondents had the same high rate of antiplatelet use as respondents. In a 1997 survey of persons with diabetes in the KPNW membership, otherwise similar nonrespondents were less likely to make and keep primary care appointments or to monitor their blood glucose level at home, although their adherence to recommended antihyperglycemic drug regimens was similar to that of respondents (J.B.B., unpublished data, June 1998).

Fortunately, in the present study, the 80% survey response (excluding persons who had moved or died)
95% item response limit the potential impact of nonresponse bias.

Finally, while members of KPNW are generally similar in age, sex, ethnicity, and economic status to the Portland metropolitan area population, they do not duplicate the US population structure. In particular, members of minority ethnic groups are underrepresented. This may limit the generalizability of our findings.

Despite their limitations, our results document that it is possible to achieve a high use of antithrombotic agents in persons diagnosed as having atherosclerotic CVD, at least in integrated medical systems. Continued efforts should be made in all settings to optimize the use of aspirin and other antithrombotic agents among all persons at high risk of atherothrombotic CVD–related events.

Accepted for publication May 8, 2001.

This study was supported by Sanofi-Synthelabo, New York, NY, and Bristol-Myers Squibb Co, Princeton, NJ.

Corresponding author and reprints: Jonathan B. Brown, MPP, PhD, Center for Health Research, 3800 N Interstate Ave, Portland, OR 97227-1110 (e-mail: jonathan.brown@kpchr.org).

REFERENCES