Aspirin and Stroke

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In this issue of Stroke, Kronmal and colleagues report the intriguing finding that in a cohort of elderly people, self-selection for aspirin use was associated with increased risks of ischemic stroke in women and hemorrhagic stroke in men and women. The authors are commendably cautious in their interpretation of the findings and raise the possibility of confounding by reasons for aspirin use as an explanation for the observed association. However, it is useful to view these findings in the context of the totality of available evidence.¹,²

Despite 100 years of widespread use, the potential for aspirin to affect risks of stroke has only been recognized relatively recently, due to the Nobel prize–winning work of Sir John Vane, who demonstrated that aspirin permanently inhibits cyclooxygenase-dependent platelet aggregation.³ Since that time, case-control and cohort studies conducted largely among middle-aged populations have suggested that individuals who self-select for aspirin therapy tend to have small (i.e., 20% to 30%) decreased risks of total and ischemic stroke.⁴ If true, such benefits would be clinically very worthwhile and would have an important public health impact. Unfortunately, however, the amount of uncontrolled and uncontrollable confounding in such studies, no matter how well designed and conducted, is likely to be as large as the effects being sought. In such circumstances, the most reliable design strategy to answer the question definitively is a large-scale randomized trial.⁵

In a collaborative worldwide overview of all randomized trials of antiplatelet agents, aspirin was shown to reduce the risk of nonfatal stroke by 25%.⁶ This reduction was a weighted average of a 31% (±5%) highly statistically significant reduction among high-risk patients with a history of occlusive disease and a possible but statistically nonsignificant 21% (±13%) increase among all low-risk patients (i.e., primary prevention). The latter uninformative null result derived primarily from inadequate numbers of stroke end points in the two completed primary prevention trials, the US Physicians’ Health Study and the British Doctors’ Trial, both of which included only men.¹ With respect to cerebral hemorrhage, the data from all these randomized trials taken together are compatible with about a 1 per 1000 excess due to aspirin, which is not surprising, as any agent that decreases clotting may increase bleeding.

In this context then, the findings of Kronmal and colleagues of a potential increase in hemorrhagic stroke among elderly men and women seems plausible. However, as the authors state, the conclusion that aspirin itself increases risk of ischemic stroke in elderly women is premature and unwarranted. The totality of evidence from basic research, observational epidemiological studies, and all randomized trials is in fact most compatible with decreased, not increased, risks of ischemic stroke due to aspirin among women as well as men, and at all ages.¹,² Moreover, issues dealing with the recording of aspirin use limit the interpretability of the findings by Kronmal et al. Because use of aspirin for only 10 of 14 days was required for a patient to be considered a “frequent user,” this category included many patients taking aspirin for reasons other than cardiovascular (cardiovascular prevention would imply 14 of 14 days’ use). In this setting, very high doses of aspirin (several grams), which may have antiatherogenic and/or thrombogenic properties, may have been taken by several of these patients (for pain or arthritis, for example). Indeed, the use of aspirin immediately before stroke may be more important than intermittent use over a few days, especially if a very high dose was taken within a few hours before stroke. Also, as only 10 of 14 days on aspirin were required for a patient to be considered a frequent user, this group may include patients who in fact stopped aspirin a few days before stroke, in the setting of previous regular use. In this case, because of the short duration of action of aspirin, ischemic stroke may have been associated with the interruption of regular aspirin treatment. Moreover, calling 1-day users “nonusers” may be misleading if that particular day was the one before the stroke and the dose of aspirin was very high.

Thus, we agree with Kronmal and colleagues that the question of aspirin for primary prevention of stroke can be settled only by randomized clinical trials. At this time among women, the only available data on aspirin and stroke derive from observational studies that tend to suggest decreases in ischemic but possible increases in hemorrhagic stroke. To evaluate directly the balance of benefits and risks of aspirin among apparently healthy women, the ongoing Women’s Health Study has randomized approximately 40,000 female health professionals aged 45 years and older. A large proportion of the strokes in this trial will occur among the elderly.

There are presently no approved prescription indications for aspirin in the primary prevention of cardiovascular disease, and any such formal policy recommendations need to await the results of the ongoing randomized trials. In the meantime, aspirin prophylaxis may nonetheless be considered...
appropriate for some individuals. The recently updated guidelines from the US Preventive Services Task Force suggest that the benefit of aspirin may outweigh the harm in men with risk factors for coronary disease who lack contraindications to aspirin use.8 The American Heart Association has made similar recommendations.2 No guidelines have been issued for women. However, while awaiting definitive data from the Women’s Health Study, the observational data in women, in conjunction with the definitive randomized trial data in male physicians, suggest that aspirin may also be beneficial in primary prevention for women whose risk of myocardial infarction is sufficiently high to warrant exposure to risks of long-term administration of this drug.

It is important to view the potential benefits of aspirin in the context of current knowledge about modification of other cardiovascular risk factors. For example, a 10% decrease in blood cholesterol corresponds to a roughly 20% to 30% reduction in risk of cardiovascular disease.9 For blood pressure, a 5- to 6-mm decrease in diastolic pressure among those with mild-to-moderate hypertension lowers risks of coronary heart disease by 14% and stroke by 42%.10 Finally, cessation of cigarette smoking results in an approximately 60% decrease in coronary heart disease, perhaps even within a matter of months.11

Thus, aspirin should always be viewed as a possible adjunct, not an alternative, to control or elimination of other cardiovascular risk factors. Aspirin therapy should be initiated only on the recommendation of a physician or other primary healthcare provider. Such a recommendation should be based on an individual clinical judgment that considers the cardiovascular risks of the patient, the adverse effects of the drug, and the documented benefits on various manifestations of cardiovascular disease in different categories of patients.

Kronmal and colleagues have added importantly relevant information to the question of aspirin and the primary prevention of stroke in the elderly, and they are to be commended for advising clinicians and the general public to await the results of ongoing randomized trials before clear recommendations can be made.

References


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