Owing to the large variability associated with this estimate of risk and to potential biases we were unable to measure or control, these data do not provide convincing evidence that aspirin is associated with increased risk of hemorrhagic stroke. However, because of the increasing prevalence of aspirin use and the twofold excess risk estimated from these clinical trials, it might be prudent to consider testing the hypothesis that aspirin use is a risk factor for hemorrhagic stroke.

Nancy E. Mayo, PhD
Adrian R. Levy, BSc
Research Department
Jewish Rehabilitation Hospital
Chomedey-Laval
Montreal, Quebec, Canada

Mark S. Goldberg, MSc
Epidemiologist
Département de Santé Communautaire
Hôpital Sacré-Cœur de Montréal
Montreal, Quebec, Canada

References

Aspirin and Hemorrhagic Stroke

To the Editor:

We have noted an increasing rate of hemorrhagic stroke in the Province of Quebec, Canada,1 and are concerned that this rise may be due in part to increased consumption of aspirin.

Recently, there has been much discussion about the use of aspirin for the primary prevention of myocardial infarction, arising mainly from findings from two recent clinical trials.2,3 Not only were these two studies discordant on the degree to which aspirin was associated with hemorrhagic strokes. In the study of British physicians,2 there was no difference in number of hemorrhagic strokes in the group taking aspirin compared with the group avoiding aspirin (relative risk [RR]=1.1). In the American Physicians' Health Study,3 the group taking aspirin experienced twice as many hemorrhagic strokes as those taking a placebo (23 cases versus 12 cases; RR=2.14, p<0.06).

Estimates of the risk of hemorrhagic stroke associated with the use of aspirin can also be gleaned from the many clinical trials evaluating the effectiveness of aspirin for the primary and secondary prevention of myocardial infarction and stroke. Clinical trials for the prevention of myocardial infarction, for the most part, did not enumerate hemorrhagic strokes as separate events and thus do not permit an opportunity to assess risk. The studies on the prevention of stroke do provide this opportunity, but in no one trial were there enough hemorrhagic events to raise concern; taken collectively, the possibility of an increased risk emerges.

In Table 1, we have compiled the findings on the occurrence of hemorrhagic stroke events from eight placebo-controlled randomized clinical trials of aspirin for the prevention of stroke. There were a total of 21 hemorrhagic strokes occurring among the 2,981 persons who were randomized to receive aspirin compared with seven hemorrhagic strokes among the 2,187 persons randomized to placebo (RR=1.93, 95% confidence interval 0.82-4.54). The confidence interval was calculated from the estimate of standard error derived using logistic regression, which modeled the logarithm of the odds of hemorrhagic stroke by assignment to aspirin or placebo groups.

TABLE 1. Frequency of Hemorrhagic Strokes in Placebo-Controlled Clinical Trials of Effectiveness of Aspirin for Prevention of Stroke

<table>
<thead>
<tr>
<th>Reference/Author/Country</th>
<th>Dose (mg/day)</th>
<th>% Male</th>
<th>Months of follow-up</th>
<th>Age (yr)</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/Atrial Fibrillation Study Group USA</td>
<td>325</td>
<td>71</td>
<td>24</td>
<td>67</td>
<td>1/517</td>
<td>0/528</td>
</tr>
<tr>
<td>7/UK-TIA Study Group</td>
<td>300, 1,200</td>
<td>73</td>
<td>48</td>
<td>60</td>
<td>13/1,621</td>
<td>3/814</td>
</tr>
<tr>
<td>8/Swedish Cooperative Study</td>
<td>1,500</td>
<td>62</td>
<td>24</td>
<td>68</td>
<td>3/253</td>
<td>2/252</td>
</tr>
<tr>
<td>9/Sorensen et al/Denmark</td>
<td>1,000</td>
<td>73</td>
<td>25</td>
<td>59</td>
<td>1/101</td>
<td>1/102</td>
</tr>
<tr>
<td>10/Bousser et al/France</td>
<td>300</td>
<td>70</td>
<td>36</td>
<td>63</td>
<td>2/198</td>
<td>2/204</td>
</tr>
<tr>
<td>11/Fields et al/USA</td>
<td>1,500</td>
<td>66</td>
<td>24</td>
<td>=45</td>
<td>1/88</td>
<td>0/90</td>
</tr>
<tr>
<td>12/Gent et al/Canada</td>
<td>1,400</td>
<td>NE</td>
<td>42</td>
<td>NE</td>
<td>0/143</td>
<td>0/137</td>
</tr>
<tr>
<td>13/Reuther and Dorndorf W. Germany</td>
<td>1,500</td>
<td>65</td>
<td>24</td>
<td>NE</td>
<td>0/60</td>
<td>0/60</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21/2,981</td>
<td>8/2,187</td>
</tr>
</tbody>
</table>

Age, mean age unless otherwise indicated; NE, not estimable.
*Warfarin group excluded.
†Two doses of aspirin.
‡Median length of follow-up.
§Group with both aspirin and dipyridamole excluded.
∥Postsurgical treatment groups excluded.
#Number of hemorrhagic strokes inferred from article.

Letters to the Editor
The Lacune Hypothesis

To the Editor:

After lengthy discussion of the definition, pathogenesis, natural history, and prognosis of lacunes, Millikan and Futrell conclude that "a lacune is a stroke, just a small one." The need for a better definition of the old label "lacune" had already been envisaged.2,4

The label lacune is attributed to the pathological lesion as such4 and should not be applied to the computed tomography (CT)–magnetic resonance imaging picture or to the clinical syndrome. Indeed, if the brain is examined at the onset of the clinical picture or shortly thereafter, the low-density area revealed by the CT scan surely cannot be related to a lacune, but to an ischemic infarction of restricted size, which usually evolves into a cavity, or more rarely, glial mesodermal scar tissue.5

I agree completely with those who hold that lacune is one of the many misleading diagnostic labels used in clinical neurology. Moreover, I would add some brief additional comments to Millikan and Futrell’s review.

I do not believe that "the neuropathologist’s and the radiologist’s definitions of a lacune are clear.6" Radiologists should give a description of the image, in terms of density level, size, shape, and location of the involved area. The term lacune is only a pathological one.

As to the pathogenesis of lacune,1 in our experience patients with lacunar lesions and related clinical syndromes were more often hypertensive than both nonvascular controls (75.3% versus 35.1%, p < 0.0005) and ischemic controls as well (75.3% versus 59.5%, p < 0.001). In normotensive patients (about 30% of cases), embolism from the large arteries or from the heart could have been responsible.6

Intracerebral small-vessel occlusion was often underestimated as a cause of ischemic lesions because, in the pathophysiology of cerebral ischemia, emphasis has been placed on the involvement of large cranial arteries rather than on the obstruction of small ones. However, intracerebral small-vessel occlusion, regardless of its origin, should be held responsible for microinfarctions, especially deep ones.7

In our experience,8 the survival rate of lacunar patients was 479/1,000, definitely lower than the survival rate of the normal population (755/1,000). The survival rate curve in patients with CT lacunar images was slightly higher than that of completed stroke due to large infarcts, but considerably lower than that of patients with reversible ischemic attacks. Life expectancy was significantly shortened if the patient was hypertensive, >65 years of age, or exhibited a poor functional recovery.

The average recurrence rate for new cerebrovascular episodes was 4.7/100 patients/year, much lower than that of survivors from cerebral infarction.

An excess of mortality was observed in patients with multiple lacunes suffering from a pseudobulbar syndrome, with poor functional recovery, poorly controlled arterial hypertension, and age >65 years.

"The common denominator for the definition of lacune, whether used by a pathologist, clinician, or radiologist, is that it’s small."1 Thus the term lacune can be replaced by the label "small stroke," or "small, deep stroke." "Confusion has come to clinical practice when the adjective form is used, as in ‘lacunar disease,’ ‘lacunar state,’ ‘lacunar syndrome,’ ‘lacunar infarction,’ and ‘lacunar stroke,’ often with the implication that these small infarcts are caused by hypertension and small-vessel disease (the ‘lacune hypothesis’)."1

I believe that lacune is only a pathological term; however, the definition "lacunar syndrome" is customarily applied to clinical pictures such as sensory strokes, pure motor hemiplegias, ataxic hemiparesis, and dysarthria–clumsy hand syndromes, in relation to small, low-density areas, as shown by CT scan. Moreover, syndromes brought about by lacunes also include reversible ischemic attacks (transient ischemic attack or reversible ischemic neurologic disease).3,4 On the other hand, the role of lacunes in bringing about dementia is debated, as is the role of multiple infarctions.9

Should the so-called lacunar syndrome be considered a misleading label, and can we substitute the term “small, deep infarction syndrome” for this term? Obviously, these small, deep strokes (how small? how deep?) still exhibit different clinical features and prognoses than larger infarctions.

Like Toole’s definitions10 of syndromes of the carotid and vertebrobasilar arteries and their branches, I would suggest the label of “syndrome of the small intracerebral arteries” for lacunar syndrome. Indeed, the definition and classification of cerebrovascular disease, mainly with respect to transient ischemic attacks and lacunes, need a thorough revision.

Carlo Loeb, MD
Department of Neurology
University of Genova
Genova, Italy

References

Aspirin and hemorrhagic stroke.
N E Mayo, A R Levy and M S Goldberg

doi: 10.1161/01.STR.22.9.1213

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
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:
http://stroke.ahajournals.org/content/22/9/1213.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at: http://stroke.ahajournals.org/subscriptions/