Aspirin in Alzheimer’s Disease
Increased Risk of Intracerebral Hemorrhage: Cause for Concern?

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Background and Purpose—In a randomized controlled trial in Alzheimer’s disease (AD), we found a higher number of intracerebral hemorrhages (ICHs) in patients randomized to aspirin treatment. Here, we evaluate the literature on the risk of ICH as a complication in patients with AD treated with aspirin.

Methods—Systematic review and comparison of the occurrence of events over time between the aspirin and control group in each trial using Cox regression analysis. Estimated hazard ratios (HRs) were combined in a pooled HR.

Results—Two randomized controlled trials on aspirin for AD were found. In the Evaluation of Vascular Care in Alzheimer’s Disease (EVA) trial (conducted in our center), 4.6% of patients in the group receiving a multicomponent treatment that included aspirin had an ICH (3/65; 95% confidence interval [CI], 1.0 to 12.9) versus 0% in the control group (0/58; 95% CI, 0 to 6.2). In the Aspirin in Alzheimer’s Disease (AD2000) trial, these proportions were, respectively, 2.6% (4/156; 95% CI, 0.7 to 6.4) and 0% (0/154; 95% CI, 0 to 2.4). The pooled proportion of ICHs in the aspirin group is 3.2% (7/221; 95% CI, 1.3 to 6.4) versus 0% in the control group (0/212; 95% CI, 0 to 1.7). The pooled HR for an ICH in AD patients using aspirin is 7.63 (95% CI, 0.72 to 81.00; P=0.09).

Conclusions—Although the number of cases in both trials is small, our findings suggest that aspirin use in AD might pose an increased risk of ICH, whereas it has no effect on cognition. If there is an unequivocal cardiovascular indication for aspirin, it should not be withheld in AD patients. (Stroke. 2010;41:00-00.)

Key Words: Alzheimer’s disease ■ aspirin ■ dementia ■ ICH ■ intracerebral hemorrhage

The previously held sharp distinction between dementia of the Alzheimer-type and vascular dementia is currently fading. The association of vascular risk factors with an increased risk of AD has fuelled the concept of “mixed dementia,” as has the finding of concomitant cerebral infarctions in addition to Alzheimer’s disease (AD) pathology in many patients with a clinical diagnosis of AD. Furthermore, neuroradiologic studies have shown that white matter lesions on MRI are common in AD patients. Inspired by this mixed dementia concept, the hypothesis has been advanced that reducing the risk of vascular events, eg, by aspirin therapy, may delay the onset of dementia and slow its progression. However, a Cochrane review concluded that there is no evidence of a protective effect of aspirin in vascular dementia, and 2 recently published randomized controlled trials on aspirin in AD reveal no effect on cognition either. Moreover, an important finding in both these trials is a substantial number of intracerebral hemorrhages (ICHs) (all spontaneous nontraumatic intraparenchymal hemorrhages) in the intervention group as a possible serious complication of aspirin, suggesting an increased susceptibility for ICH in AD patients treated with aspirin.

In this brief review we will explore this risk and aim to put it into context by presenting a systematic review and pooled data analysis.

Methods

For this review, we searched PubMed and the Cochrane Library until October 2009. We used the limits “English language” and “human subjects” and combinations of the Medical Subject Headings (MeSH) “Alzheimer disease,” “aspirin,” “intracranial hemorrhage,” and “cerebral hemorrhage.” We excluded traumatic cerebral hemorrhages. This search was supplemented from the bibliography of the retrieved articles. All randomized controlled trials are included that investigated the effect of aspirin for AD and also registered complications of aspirin therapy including ICH.

For statistical analysis, we compared the occurrence of events over time between the aspirin and control group in each trial using a Cox regression. We used Firth’s penalized likelihood estimation, yielding a finite estimate of the hazard ratio (HR) for each trial (despite the presence of 0 events in the control groups). To determine time of follow-up, we used individual patient data for the Evaluation

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of Vascular Care in Alzheimer’s Disease (EVA) trial. For the Aspirin in Alzheimer’s Disease (AD2000) trial, we estimated the time of follow-up on the basis of available numbers of patients who were still available for assessment at certain follow-up times (12 weeks, 1 year, 2 years, 3 years), as described in the report. The estimated HRs and SEs were combined in a pooled HR. In all analyses, statistical uncertainties were expressed in 95% confidence intervals (CIs). Probability values of <0.05 indicate statistical significance. To compare the results with a recent metaanalysis on aspirin therapy and an observational cohort study on aspirin therapy in a specifically elderly population, we calculated the number of events per 1000 patient years.

Results

Only 2 randomized controlled trials on aspirin for AD were found, including the trial conducted in our center (EVA). The aim of the EVA trial was to investigate whether vascular care could slow dementia progression of patients with AD. Patients randomized to vascular care were subjected to a series of vascular risk–stratifying measures, including therapy with acetylsalicylic acid (38 to 100 mg once a day). Primary outcome was disability and mean time of follow-up was 22 months. In the AD2000 trial, open-label aspirin therapy (75 mg per day) was compared with aspirin avoidance. Primary outcome measures were cognition and functional outcome. Mean time of follow-up was 29 months. Both trials failed to document any disease-modifying effect.

The proportion of patients with an ICH in the intervention group of the EVA trial was 4.6% (3/65) versus 0% (0/58) in the control group, and in the AD2000 trial, these proportions were, respectively, 2.6% (4/156) and 0% (0/154); the pooled proportion of ICHs in the aspirin group is 3.2% (7/221) (Table). The pooled HR for an ICH in AD patients using aspirin is 7.63 (95% CI, 0.72 to 81.00; P = 0.09). All patients with an ICH reported to be compliant with the prescribed aspirin at the time of hemorrhage. There was no difference in mortality and cardiac events between the groups in both trials.

The number of events per 1000 patient years in the EVA trial was 26 (3/116 patient years; 95% CI, 5 to 74). For the AD2000 trial, this number was 11 (4/379 patient years; 95% CI, 3 to 27). To rank the estimated risk of ICH in the AD population, we compared it with the results of a recent metaanalysis by the Antithrombotic Trialists’ Collaboration (ATT) on aspirin in primary prevention (95 000 individuals; 660 000 person years; mean age, 56 years) and secondary prevention (17 000 individuals; 43 000 person years; mean age, 58 years) of vascular disease and the Cardiovascular Health Study (CHS), an observational cohort study on aspirin therapy in a specifically elderly population (5011 individuals; mean age, 72 years). The mean age in the EVA trial is 76 years; the median age in the AD2000 trial is 74 years. Both advanced age and AD seem to increase the risk of ICH in patients using aspirin (Figure).

Discussion

Our pooled analysis of 2 randomized studies indicates a possibly increased risk of ICH in AD patients using low-dose aspirin. The small number of events in our analysis (7 ICHs in total) is an important limitation, and the increase in ICH was not statistically significant (P = 0.09). Nevertheless, the proportion experiencing ICH (3.2%) is relatively high. This finding of a possibly increased risk of ICH in AD patients is particularly relevant given the hypothesized beneficial effects of treating vascular risk factors in demented patients, eg, by aspirin therapy.

Because aspirin therapy was among several vascular risk–stratifying measures in the EVA trial, it is technically impossible to attribute the hypothesized increased risk of ICH in this study to aspirin alone. The use of statins has also been linked to ICH. In the EVA trial, however, none of the 3 patients experiencing an ICH was on statin therapy, excluding statin use as a potential contributor to the increased risk of ICH in these cases. In addition, neither coumarin derivates nor additional antiplatelet agents were used by any of the 7 patients that had an ICH.

A possible reason for an increased risk of ICH in AD could be that cerebral amyloid angiopathy, a common pathological

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Table. Numbers of ICHs and Numbers of Patients Randomized in Each Group, Mean Time of Follow-Up per Patient, and HR With 95% CI

<table>
<thead>
<tr>
<th>Group</th>
<th>n of Events</th>
<th>%</th>
<th>n of Events</th>
<th>%</th>
<th>Mean Time of Follow-Up (Months)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA</td>
<td>3/65</td>
<td>4.6</td>
<td>0/58</td>
<td>0</td>
<td>22</td>
<td>6.48 (0.21–198.48)</td>
<td>0.13</td>
</tr>
<tr>
<td>AD2000</td>
<td>4/156</td>
<td>2.6</td>
<td>0/154</td>
<td>0</td>
<td>29</td>
<td>8.85 (0.34–231.98)</td>
<td>0.06</td>
</tr>
<tr>
<td>Pooled</td>
<td>7/221</td>
<td>3.2</td>
<td>0/212</td>
<td>0</td>
<td>27</td>
<td>7.63 (0.72–81.00)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

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Figure. Number of ICH per 1000 patient years in aspirin-taking patients for the EVA, AD2000, CHS, and ATT studies with the secondary prevention part (S) and primary prevention part (P). 95% confidence intervals are indicated by vertically capped lines.
finding in AD patients, may render patients prone to ICH. The high prevalence of AD-associated microbleeds, an expression of amyloid angiopathy on neuroimaging, supports this hypothesis. The presence of these microbleeds, and perhaps other MRI characteristics, could potentially be used to identify patients particularly at risk for developing ICH.

The present analysis falls short of providing a sound basis for recommendations against the use of aspirin in AD. In case of a conventional indication for aspirin as a secondary prevention measure (eg, after stroke or myocardial infarction), aspirin should be prescribed also in patients with AD. However, with the results of our study suggesting an increased risk for ICH, we want to stress that aspirin should not be prescribed for AD patients to slow cognitive decline if no clear cardiovascular indication exists. More relevant data on this topic are needed, and the data from existing large prospective cohort studies could potentially give more insight in the risk of ICH in patients with AD taking aspirin.

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