Randomized Controlled Trial of Acetylsalicylic Acid in Aneurysmal Subarachnoid Hemorrhage

The MASH Study

Walter M. van den Bergh, MD; on behalf of the MASH Study Group

Background and Purpose—A previous systematic review of randomized trials suggested a positive effect of antiplatelet therapy in patients with aneurysmal subarachnoid hemorrhage (SAH). We performed a randomized controlled trial to assess whether acetylsalicylic acid (ASA) reduces the risk of delayed ischemic neurological deficit (DIND) in patients with SAH.

Methods—Criteria for inclusion were aneurysm treatment within 4 days after SAH. Trial medication (14 daily suppositories with 100 mg ASA or placebo) was started within 12 hours after aneurysm treatment. Analysis for the primary outcome event DIND was made according to the “on-treatment” principle and for the secondary outcome measures “poor outcome” and “nonexcellent outcome” according to the “intention-to-treat” principle.

Results—Inclusion was stopped after the second interim analysis, when 161 of the planned 200 patients were included, because by then the chances of a positive effect were negligible. At the final analysis, ASA did not reduce the risk of DIND (hazard ratio, 1.83; 95% CI, 0.85 to 3.9). The relative risk reduction for poor outcome was 21% (relative risk, 0.79; 95% CI, 0.38 to 1.6).

Conclusions—ASA given after aneurysm treatment does not appreciably reduce the occurrence of DIND. (Stroke. 2006;37:2326-2330.)

Key Words: aspirin | ischemia | platelets | randomized controlled trials | subarachnoid hemorrhage

Because of its occurrence at a young age and its often poor outcome, subarachnoid hemorrhage (SAH) causes as great a loss of productive life years as does ischemic stroke, the most common form of stroke.1 Delayed ischemic neurological deficit (DIND), occurring most often between 4 and 10 days after the hemorrhage, is an important cause of death and dependence after SAH. The current mainstay of treatment is nimodipine and maintaining normovolemia, but even with this strategy, improvement in clinical outcome has been modest.2

A number of studies indicate a possible role for increased platelet activity in the development of SAH-induced vasospasm and DIND. Platelet aggregation and the associated release of thromboxane B2, the stable metabolite of thromboxane A2, are increased from day 3 after SAH, especially in patients with symptoms of DIND.3,4 Thromboxane A2, synthesized from activated platelets, is a potent vasoconstrictor. Data from animal research further support a role for platelet aggregation. Both rupture of an artery and the presence of blood at the abluminal side of an intact artery activate platelet aggregation.5 Moreover, the antiplatelet activity of the endothelium is reduced after SAH.6

Acetylsalicylic acid (ASA) is a well-known inhibitor of platelet aggregation.7 ASA acetylates cyclooxygenase and thereby inhibits platelet production of thromboxane A2. In an observational study of a consecutive series of patients with SAH, those with salicylates in urine samples on admission had a reduced risk of cerebral infarction and ischemic symptoms.8 These observations suggest that platelet function may be associated with DIND after aneurysmal SAH and that the administration of platelet inhibitors might have a preventive effect on the development of DIND and thereby on outcome after SAH.

Previously, we reported on a randomized, placebo-controlled pilot study of postoperative administration of ASA in 50 patients who underwent operation of the aneurysm within 96 hours after SAH.9 The results of that pilot study suggested that ASA administration in SAH is feasible and safe. We also performed a meta-analysis of all randomized clinical trials on platelet aggregation inhibitors in patients with SAH.10 Five trials totaling 699 patients were included. The results showed a reduction of DIND and a tendency toward better outcome in patients treated with platelet inhibitors.

In this article, we report on a randomized, placebo-controlled trial to assess whether ASA, started when aneurysm treatment is performed within 4 days after SAH onset, reduces the frequency of DIND in patients with aneurysmal SAH.
Methods
Between November 2000 and January 2004, we enrolled patients in the Magnesium and Acetylsalicylic acid in Subarachnoid Hemorrhage (MASH) trial. The MASH trial was a randomized clinical trial with a factorial design: magnesium versus placebo and ASA versus placebo (separated a priori). Patients were included when they could be randomized within 4 days after aneurysmal SAH. Patients with hypersensitivity to ASA, recent ASA use, or age <18 years were not included. The diagnosis of SAH was based on a positive computed tomography (CT) scan or xanthochromia of cerebrospinal fluid. Aneurysmal SAH was diagnosed if an aneurysm was present on angiography or if the CT scan showed a typical aneurysmal pattern of hemorrhage. If the CT scan was negative, xanthochromia of cerebrospinal fluid with an aneurysm on angiography confirmed the diagnosis of aneurysmal SAH. Informed consent was obtained for both the magnesium and the ASA part of the study at the same time, as soon after admission as possible, and before occlusion of the aneurysm. After informed consent was obtained, patients started with the magnesium part of the study immediately. Thus, all 283 patients included in the study participated in the magnesium part of the trial. Enrollment in the ASA part of study was deferred until the aneurysm had been occluded. If occlusion of the aneurysm was performed later than 4 days after the hemorrhage, patients were not enrolled in that part of the study. Eventually, only 161 of the 283 included patients could be enrolled in the ASA part of the study.

Only the results of the ASA part of the trial are presented here, those on magnesium were reported previously. The ethics committee of the participating hospitals approved the protocol of the trial. The clinical condition at admission was assessed with the World Federation of Neurological Surgeons (WFNS) scale. We assessed the amount of extravasated blood on the initial CT scan according to the method described by Hijdra et al.

All patients were kept under close observation with continuous monitoring of blood pressure, heart rate, ECG, and arterial oxygen saturation for at least 2 weeks after the onset of SAH. They were treated according to a standardized protocol that consisted of absolute bed rest until aneurysm treatment, administration of nimodipine, cessation of antihypertensive medication, and intravenous administration of fluid aiming for normovolemia.

Interventions
Blinded allocation of trial medication was done by means of a consecutive series of numbered boxes, containing either ASA or placebo. We started the trial medication, which consisted of 14 daily suppositories with either 100 mg ASA or placebo, within 12 hours after aneurysm occlusion. The dose regimen was based on a dose-finding study in healthy volunteers that found a reduction of >99% in thromboxane B2 synthesis after 5 days of 100-mg ASA suppositories.

Data Collection
All CT scans made after SAH onset were analyzed for new hypodensities and postoperative hemorrhage by at least 3 members of the steering committee, always in the presence of the principal investigators (W.M.B., G.J.E.R.). Hypodensities on CT scan were classified according to the presumed origin, as follows: (1) representing “spontaneous” cerebral ischemia; (2) caused by operation or endovascular treatment; (3) associated with an intracerebral hematoma; (4) caused by placement of a ventricular catheter; and (5) other. Patients with an uneventful clinical course in whom no control CT scan was made were rated as having no new hypodensities or postoperative hemorrhages. Three months after the SAH, we assessed functional outcome with the modified Rankin Scale (mRS) by means of a telephone interview.

Outcome Measures
The predefined primary outcome measure was the occurrence of DIND within 3 months after the onset of SAH. This primary outcome event was defined as the occurrence of a new, spontaneous, hypodense lesion on CT that was accompanied by new clinical features of DIND (gradually developed focal deficits, decreased level of consciousness, or both). The reference scan was the initial diagnostic CT scan.

Secondary predefined outcome measures were (1) the occurrence of any new hypodensity on brain CT, regardless of its cause; (2) postoperative hemorrhage; (3) poor outcome (mRS ≥4); and (4) nonexcellent outcome (mRS ≥1). With a Rankin score of 0 (excellent outcome), the patient is considered to have no symptoms and no reduction in quality of life.

Data Analysis
Trial design and conduct for the primary outcome and for the secondary outcome event “any hypodensity on CT” was according to the “on-treatment” principle, because this was an explanatory research question. The secondary outcome measures “poor outcome” and “nonexcellent outcome” were analyzed according to the “intention-to-treat” principle, because these criteria are most relevant from the perspective of the patient.

According to the data of our pilot study, 50% of patients in the untreated group could be expected to have hypodense lesions on CT. Assuming that intervention reduces this risk by 40%, with the usual α=5% and 1−β=80%, 200 patients were needed. The risks of DIND in the 2 groups were compared in terms of the hazard ratio, with corresponding 95% CIs obtained from Cox proportional-hazards modeling. To assess the effect of treatment on outcome at 3 months, we estimated risk ratios (RRs) with corresponding 95% CIs. Predefined adjusted analyses were performed for endovascular versus surgical aneurysm treatment.

Results
On the basis of data of the second interim analysis (performed after randomization of 121 patients), the Data Monitoring Committee advised that inclusion be discontinued because the chance of finding a positive effect for the primary outcome event DIND was <1%. The Steering Committee terminated the study.

At that time, 161 patients had been randomized (the Figure). Patients in the ASA and control groups were comparable at baseline (Table 1). In the explanatory, on-treatment analysis, ASA tended to increase the risk of DIND (hazard ratio, 1.83; 95% CI, 0.85 to 3.9; Table 2). The RR for the outcome event “any new hypodensities on CT, regardless of cause” was 1.06 (95% CI, 0.75 to 1.5). In the intention-to-treat analysis, the RR reduction for poor outcome at 3 months was 21% (RR, 0.79; 95% CI, 0.38 to 1.6). The relative chance for excellent outcome was 0.60 (95% CI, 0.24 to 1.5).

Patients in whom aneurysm occlusion was achieved by endovascular treatment more often initially had a worse neurological condition (WFNS ≥4) than those with a surgically treated aneurysm: 25% versus 12%. The increased RR for DIND with ASA treatment was less in patients with endovascular treatment than for those in whom neurosurgical treatment was performed (1.4 versus 1.9). Moreover, the nonsignificant tendency toward risk reduction of poor outcome by ASA was greater after embolization than after surgical treatment (RR, 0.71 versus 0.81).

Discussion
This trial did not confirm a beneficial effect of rectal ASA administration within the first days after treatment of a ruptured intracranial aneurysm on the occurrence of DIND; it even showed a trend toward a negative effect. Despite this
negative effect for DIND, functional outcome in patients who received ASA tended to be better. For both clinical outcome measures, no statistically significant result was obtained, and CIs were wide.

Our study result seems to contradict the effect on DIND attributed to ASA in the systematic review of previous randomized, controlled trials and in observational studies. We have no outright explanation for the lack of effect in the present study, but 5 possible factors should be mentioned. First, the positive trends in the original meta-analysis were based on all antiplatelet drugs combined; the data for ASA alone were still rather imprecise and hence, compatible with no effect. Second, ASA may not be the right antiplatelet drug to prevent DIND. In our meta-analysis of randomized studies conducted before the current trial, antiplatelet drugs were found to reduce both DIND and poor outcome, although the beneficial effect on DIND was mainly based on studies with antiplatelet drugs other than ASA. A third explanation may be the dosage of ASA. Our medication dosage was based on a pilot study in healthy volunteers. In SAH patients, a daily dose of 100 mg might not be sufficient. We have no information whether, for example, endothelial thromboxane was also inhibited. In the only 2 previous studies with ASA, the dosages were 100 and 600 mg, but both studies had small numbers of patients and showed no or only marginal beneficial effect. A fourth explanation may be patient selection. In our study, patients were randomized only if aneurysm treatment was performed within 4 days after hemorrhage. Patient selection for early surgery was predominantly based on a good neurological condition. This results in a study population with a low risk for DIND and poor outcome. This makes it more difficult to find a beneficial effect of ASA in patients in whom the aneurysm was treated surgically, which was the case in the majority of patients (67%) in this study. Good clinical condition was not required for patients suitable for endovascular treatment, and that might be the reason that the trend toward a negative effect of ASA on DIND was less evident in patients who were treated via the endovascular route. A fifth explanation may be the timing of drug administration. In observational studies on the effects of ASA in patients with SAH, ASA was part of the medication in patients before the onset of SAH, so the beneficial effects in these patients might have been caused by reducing the ischemic cascade caused by the initial hemorrhage. Preoperative administration of ASA is discouraged because of the proposed risk of hemorrhagic complications during operation. ASA may also induce rebleeding or may have a detrimental effect in case of rebleeding.

The data of our study are compatible with a better outcome for patients treated with ASA. This benefit is difficult to explain because it is unlikely mediated by a reduction in DIND. Perhaps ASA decreases the occurrence of microemboli after SAH. Microemboli occur for an extended period of time and might be boosted by surgical or endovascular procedures. Microemboli might be too small to cause DIND but perhaps have an effect on outcome.

Our study provides no evidence for the routine use of ASA after endovascular aneurysm occlusion to prevent DIND, although the tendency toward an increased RR for DIND with ASA treatment was less in patients with endovascular treatment than those in whom neurosurgical treatment was performed. Similarly, the tendency toward a decreased risk of poor outcome with ASA was greater after endovascular treatment than after surgical treatment.

Even if ASA treatment results in a better clinical outcome, the effect is smaller than suggested by the previous meta-analysis and probably not through reducing DIND. The relatively small point estimate indicates that a phase III trial should include large numbers of patients. When a power analysis is based on this study, ~2700 patients will be needed. Because endovascular
Appendix


Participating centers and investigators (No. of enrolled patients per center): University Medical Center Utrecht, Utrecht, The Netherlands (216): Departments of Neurosurgery (W. M. van den Bergh, J.W. Berkelbach van der Sprenkel), Neurology (W.M. van den Bergh, G.J.E. Rinkel, A. Algra, J. van Gijn, M. van Buuren, S.M. Dorhout Mees), Pharmacy (E.V. Uijtendaal), and Julius Center for Health Sciences and Primary Care (A. Algra); Erasmus Medical Center, Rotterdam, The Netherlands (40): Department of Neurology (S.L.M. Bakker, M. van der Jagt, F. van Kooten); VU University Medical Center, Amsterdam, The Netherlands (20): Department of Neurosurgery (K.W. Albrecht), and Neurology (M. Vermeulen).

**TABLE 1. Baseline and Outcome Data According to Allocated Treatment**

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Total, n=161</th>
<th>Intention-to-Treat, n=161</th>
<th>On-Treatment, n=153</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. randomized</td>
<td>161</td>
<td>87</td>
<td>83</td>
</tr>
<tr>
<td>Mean age</td>
<td>53</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Women</td>
<td>127 (79%)</td>
<td>68 (78%)</td>
<td>65 (78%)</td>
</tr>
<tr>
<td>Clinical condition at admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WFNS I</td>
<td>94 (58%)</td>
<td>54 (62%)</td>
<td>50 (60%)</td>
</tr>
<tr>
<td>WFNS II</td>
<td>38 (24%)</td>
<td>18 (21%)</td>
<td>18 (22%)</td>
</tr>
<tr>
<td>WFNS III</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>WFNS IV</td>
<td>15 (9%)</td>
<td>7 (8%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>WFNS V</td>
<td>11 (7%)</td>
<td>8 (9%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>No. of patients with cisternal blood above median (26)</td>
<td>92 (58%)</td>
<td>51 (60%)</td>
<td>49 (61%)</td>
</tr>
<tr>
<td>No. of patients with ventricular blood above median (2)</td>
<td>43 (27%)</td>
<td>24 (28%)</td>
<td>24 (29%)</td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
<td>5 (3%)</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Treatment for aneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>108 (67%)</td>
<td>53 (61%)</td>
<td>51 (61%)</td>
</tr>
<tr>
<td>Endovascular</td>
<td>52 (32%)</td>
<td>33 (38%)</td>
<td>32 (39%)</td>
</tr>
<tr>
<td>None</td>
<td>1 (1%)*</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Medication, no. of days</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Recurrent aneurysmal hemorrhage</td>
<td>9 (6%)</td>
<td>6 (7%)</td>
<td>6 (7%)</td>
</tr>
</tbody>
</table>

**Outcome measures**

| DIND | 31 (19%) | 20 (23%) | 11 (15%) | 20 (24%) | 10 (14%) |
| New hypodensities on CT | 73 (45%) | 41 (47%) | 32 (43%) | 39 (47%) | 31 (44%) |
| Case fatality | 16 (10%) | 9 (10%) | 7 (9%) | 9 (11%) | 7 (10%) |
| Poor outcome (mRS ≥4) | 25 (16%) | 12 (14%) | 13 (18%) | 12 (15%) | 12 (17%) |
| Excellent outcome (mRS=0) | 17 (11%) | 7 (8%) | 10 (14%) | 7 (8%) | 7 (10%) |
| Postoperative hematoma | 3 (2%) | 2 (2%) | 1 (1%) | 1 (1%) | 1 (1%) |

*Study medication was accidentally started before aneurysm treatment.

**TABLE 2. Outcomes in the Trial According to ASA Treatment**

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIND*</td>
<td>1.83 (0.65–3.9)</td>
</tr>
</tbody>
</table>

Secondary outcomes

| New hypodensities on CT | 1.06 (0.75–1.5) | 1.09 (0.77–1.5) |
| Poor outcome | 0.84 (0.40–1.8) | 0.79 (0.38–1.6) |
| Excellent outcome | 0.84 (0.31–2.2) | 0.60 (0.24–1.5) |

Poor outcome is defined as a Rankin score of 4 or worse. Excellent outcome is defined as a Rankin score of 0; this is a positive outcome with an RR >1 if treatment is beneficial.

*Hazard Ratio.
Source of Funding
We gratefully acknowledge the Netherlands Heart Foundation (grant 99.107) for financially supporting this study. Prof Rinkel was clinical established investigator of the Netherlands Heart Foundation (grant D98.014).

Disclosures
None.

References
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Stroke. 2006;37:2326-2330; originally published online August 3, 2006;
doi: 10.1161/01.STR.0000236841.16055.0f

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

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