Effect of Antiplatelet Therapy for Endovascular Coiling in Aneurysmal Subarachnoid Hemorrhage

Walter M. van den Bergh, MD, PhD; Richard S.C. Kerr, MD; Ale Algra, MD; Gabriel J.E. Rinkel, MD; Andrew J. Molyneux, MD, PhD; for the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group

Background and Purpose—Antiplatelets are frequently used during or after endovascular coiling of aneurysm in patients with subarachnoid hemorrhage (SAH). This strategy is based on uncontrolled case series including also patients with unruptured aneurysms or other lesions. We collected data on effectiveness of antiplatelets in patients with SAH.

Methods—All 43 participating centers in the International Subarachnoid Aneurysm Trial (ISAT) were sent a questionnaire whether they never, sometimes, or always prescribed antiplatelets during or after coiling. Based on individual patient data, the relative risks (RRs) of coiling versus clipping were calculated separately for patients treated in hospitals with standard prescription during or after coiling versus patients treated in hospitals with no standard prescription of antiplatelets. We calculated ratios of RRs for standard versus not standard prescription of antiplatelets during and for standard versus not standard prescription after coiling.

Results—Nineteen centers responded, representing 1422 (66%) of the 2143 ISAT patients. Antiplatelets were standard prescribed during coiling in 2 responding centers (8% of coiled patients) and after coiling in 6 centers (24%). For poor outcome at 2 months of coiling versus clipping the RR was 0.82 (95% CI: 0.45 to 1.49) in hospitals with a policy of antiplatelet prescription during coiling versus 0.66 (95% CI: 0.55 to 0.78) in those without such policy (ratio of RR’s 1.24, P=0.56). The ratio of RRs for 1-year outcome was 1.01 (P=0.89) for antiplatelet use during coiling and 1.00 (P=0.77) for use after coiling.

Conclusion—The results of this study do not support the assumption that antiplatelets during or after endovascular coiling improve outcome in patients with SAH. (Stroke. 2009;40:1969-1972.)

Key Words: aneurysms ■ antiplatelet drugs ■ endovascular treatment ■ subarachnoid hemorrhage

Endovascular treatment of aneurysms carries a risk of thromboembolic complications. Antiplatelets may prevent such complications and are therefore used in some but not all centers during or after endovascular embolization of cerebral aneurysms. Most data on this strategy comes from uncontrolled case series that included patients with a mixed bag of lesions, such as ruptured aneurysms, unruptured aneurysms, and AVM’s, and often also several endovascular strategies other than coiling. Thus, there is very little data on the effectiveness of antiplatelets in patients with unruptured subarachnoid hemorrhage (SAH). A Cochrane review on the use of antiplatelets after SAH showed a trend toward a better outcome in patients treated with antiplatelets, but in most patients included in the review the aneurysm had been treated by surgical clipping. In only one trial, which used acetylsalicylic acid as antiplatelet agent, part of the patients had been treated by endovascular embolization. Analysis of this subset of 52 patients showed a relative risk of 0.7 for death or dependence in favor of acetylsalicylic acid, but the 95% confidence interval was wide and ranged from 0.2 to 2.9.

The results of the International Subarachnoid Aneurysm Trial (ISAT) indicate that in patients with ruptured intracranial aneurysms suitable for both treatments, coiling of the aneurysm is more likely to result in survival free of disability 1 year after the SAH than neurosurgical clipping. If indeed antiplatelets improve outcome after SAH, the better outcome after coiling observed in ISAT may in part be explained by the use of antiplatelet after coiling in some of the participating centers, because antiplatelets are typically not prescribed after neurosurgical treatment.

The purpose of this study was to assess whether the benefit of endovascular treatment, compared to neurosurgical clipping, is influenced by use of antiplatelets after coiling. We therefore compared in patients treated within ISAT whether the reduction in poor outcome by coiling is greater when

Received June 15, 2008; final revision received September 7, 2008; accepted October 23, 2008.

From the Departments of Intensive Care (W.M.v.d.B.), Rudolf Magnus Institute of Neuroscience, and the Department of Neurology (A.A., G.J.E.R.) and Julius Center for Health Sciences and Primary Care (A.A.), University Medical Center Utrecht, The Netherlands; and the Neurovascular Research Unit (R.S.C.K., A.J.M.), Radcliffe Infirmary, Oxford, UK.

Correspondence to W.M. van den Bergh, MD, PhD; Department of Intensive Care, Room Q04.460, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands, E-mail w.m.vandenbergh@umcutrecht.nl

© 2009 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.108.528802

1969
antiplatelets are standard used during or after coiling than when antiplatelets are not standard used.

Patients and Methods

The ISAT trial enrolled 2143 patients with ruptured intracranial aneurysms and randomly assigned them to neurosurgical clipping (n=1070) or endovascular treatment by detachable platinum coils (n=1073). Recruitment started in 1997 and stopped at May 2, 2002. The results of this study were published previously. In 2007 all 43 participating centers in ISAT were sent a questionnaire whether they had never, sometimes, or always used antiplatelets during or after endovascular embolization during ISAT, and if so, which agent, which dose, and for how long. The results of this questionnaire were combined with the data in the ISAT database.

We recorded age, gender, clinical grade on the World Federation of Neurological Surgeons (WFNS) grading scale, and amount of blood on the initial CT scan by means of the Fisher score. The occurrence of delayed ischemic neurological deficit was based on a positive answer at the questionnaire if vasospasm or a thromboembolic complication has occurred. Poor outcome was defined as a modified Rankin score equal or larger than 3.

Analyses were performed for actual treatment with neurosurgical clipping or endovascular coil instead of allocation to treatment. Relative risks (RR) for endovascular coil for poor outcome after 2 months and 1 year were calculated based on the individual patient data of ISAT. The RR of coiling versus clipping were calculated separately for patients treated in hospitals that used antiplatelets as a standard during or after coiling versus patients treated in hospitals that used antiplatelets never or sometimes. Separate analyses were performed for the use of antiplatelets during and after coiling.

If the RRs for coiling versus clipping were similar for patients treated in hospitals with standard prescription of antiplatelets and patients treated in hospitals not standard prescribing antiplatelets during or after coiling, than no effect of antiplatelets is assumed. To assess the extent of the difference in relative risks between hospitals that did standard prescribe antiplatelets versus those that did not, we calculated ratios of RRs with corresponding probability values by means of logistic regression. A ratio below 1 implicates that patients benefit from the standard use of antiplatelets during or after endovascular coil.

We performed a subanalysis for patients with aneurysm treatment within 4 days after the SAH. We also calculated RRs and subsequent ratios of RR’s of coiling versus clipping for patients treated in hospitals that used antiplatelets as a standard or sometimes during or after coiling versus patients treated in hospitals that never used antiplatelets. The main reason for this secondary outcome measurement was to perform a sensitivity analysis.

Results

Nineteen of the 43 centers responded, representing 1422 (66%) of the 2143 patients originally randomized for ISAT. Of those 1422 patients, 720 underwent endovascular coil and 675 neurosurgical clipping (Figure). The baseline characteristics of the 1395 patients who actually underwent aneurysm treatment are shown in Table 1.

No antiplatelets were prescribed after neurosurgical clipping in any of the responding centers. According to the questionnaire, standard prescription of antiplatelets during coiling was done in 2 of the 19 responding centers, which comprised 8% of the coiled patients in the responding centers. Standard prescription of antiplatelets after coiling was done in 6 centers, representing 24% of the research population (Table 2). Of the 9 centers that reported to prescribe always or sometimes antiplatelets during embolization, 7 used acetylsalicylic acid (75 to 1000 mg p.o. or intravenous) and 2 abciximab (as an intravenous bolus of 250 micrograms per kilogram of body weight). All 18 centers that reported to prescribe antiplatelets after embolization used acetylsalicylic acid (75 to 325 mg p.o.) for a period ranging from 2 weeks to 6
months. Two centers reported to add clopidogrel (375 mg p.o.) to aspirin when a stent had been used.

In the subset of patients treated in the centers that responded to the questionnaire, the RR of poor outcome for patients treated with endovascular coiling versus those treated with neurosurgical clipping was 0.67 (0.57 to 0.79) after 2 months and 0.74 (0.62 to 0.89) after 1 year (Table 3), which is essentially the same as the overall results of ISAT. The relative risk ratio for poor outcome of standard use of antiplatelets during coiling was 1.24 (P=0.56) after 2 months and 1.01 (P=0.89) after 1 year. The relative risk ratios for poor outcome of antiplatelets after coiling were 1.23 (P=0.44) after 2 months and 1.00 (P=0.77) after 1 year. When the analyses were restricted to patients with aneurysm treatment within 4 days (n=893 of which 403 with endovascular coiling) the results remained essentially the same.

The secondary analysis comparing coiling versus clipping for patients treated in hospitals that always or sometimes used antiplatelets during coiling versus patients treated in hospitals that never used antiplatelets during coiling showed a relative risk ratio for poor outcome after coiling of 1.13 (P=0.27) after 2 months and 1.19 (P=0.77) after 1 year. The relative RRs for use of antiplatelets after coiling could not be performed because only 1 center representing 1 patient reported never to use antiplatelets after coiling (data not shown).

### Discussion

The results provide no support for the hypothesis that the beneficial effect of coiling after SAH over surgical clipping can be attributed to the standard prescription of antiplatelets during or after the endovascular procedure. Similarly, the results do not support the use of antiplatelets during or after coiling of ruptured aneurysms.

The major limitation of this study is that it is a posthoc analysis of a subset of the ISAT study population, which is not an ideal method to evaluate whether a policy of prescribing antiplatelets after coiling of intracranial aneurysms improves outcome in SAH. However, it is unlikely that a randomized controlled trial will ever be performed to answer this question, so we must rely on less robust evidence. Profiting from variations in care attributable to local “tradition” is a very reasonable opportunity to evaluate the efficacy of treatments, because it almost mimics the design of cluster randomized controlled trials.

Although less than half the centers responded to the questionnaire, these centers contributed 66% of the patients enrolled in ISAT. The primary outcome for this subgroup of patients is essentially the same as that for all patients randomized for the ISAT trial, which suggest that this subgroup is representative for the overall ISAT population.

A relative large proportion of responding centers indicated that they “sometimes” prescribed antiplatelets during or after coiling, which means that in the subgroup of patients who had no-standard prescription of antiplatelets, some in fact did use antiplatelets. The antiplatelet treatment contrast thus diminished. However, in the ISAT study, the overall reported coil migration and thromboembolic complications during coiling, which was presumably the indication for the use of antiplatelets in most instances in centers that sometimes used antiplatelets, was less than 2%. Interestingly, in the centers that reported to prescribe antiplatelets as a standard during endovascular coiling no thromboembolic problems were reported. The occurrence of thromboembolic problems during endovascular coiling, however, had no statistical significant effect on outcome. Moreover, the sensitivity analyses comparing always versus never or sometimes use of antiplatelets also showed no effect on outcome in favor of antiplatelets, thus making the primary results more valid.

In only two-thirds of patients aneurysm treatment was performed within 4 days after the SAH. Initiation of antiplatelet treatment after that period is less likely to have an effect on outcome by preventing thromboembolic complications or delayed ischemic neurological deficit. However, in the subgroup of patients with aneurysm treatment within 4 days the results do not differ from the overall results, indicating that timing of aneurysm treatment did not influence the results. Patients randomized for ISAT had a relatively good clinical condition at the time of randomization. The results of this study can thus not be extrapolated to the increasing number of patients with early aneurysm treatment despite a poor clinical condition.

### Table 3. Risk for Poor Outcome in Patients Treated With Endovascular Coiling Compared With Neurosurgical Clipping

<table>
<thead>
<tr>
<th></th>
<th>Poor Outcome 2 Months</th>
<th></th>
<th>Poor Outcome 1 Year</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk (95% CI)</td>
<td>Risk Ratio (P Value)</td>
<td>Relative Risk (95% CI)</td>
<td>Risk Ratio (P Value)</td>
</tr>
<tr>
<td>All treated patients (n=1395)</td>
<td>0.67 (0.57–0.79)</td>
<td>0.74 (0.62–0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital strategy during embolization (n=720)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never or sometimes antiplatelets (n=664)</td>
<td>0.66 (0.55–0.78)</td>
<td>0.74 (0.61–0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always antiplatelets (n=56)</td>
<td>0.82 (0.45–1.49)</td>
<td>1.24 (0.56)</td>
<td>0.75 (0.41–1.38)</td>
<td>1.01 (0.89)</td>
</tr>
<tr>
<td>Hospital strategy after embolization (n=720)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never or sometimes antiplatelets (n=550)</td>
<td>0.64 (0.52–0.77)</td>
<td>0.74 (0.61–0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always antiplatelets (n=170)</td>
<td>0.79 (0.57–1.10)</td>
<td>1.23 (0.44)</td>
<td>0.74 (0.51–1.07)</td>
<td>1.00 (0.77)</td>
</tr>
</tbody>
</table>
Our analyses provide no evidence that the standard prescription of antiplatelets during or after endovascular coiling further improve outcome after 2 months or 1 year. There is also no indication that the use of antiplatelets has a negative effect on outcome, eg, by an increased risk of intracranial bleeding complications as has been the case with enoxaparin after surgical occlusion of ruptured aneurysms.11

In conclusion there is no indication that the use of antiplatelets during or after endovascular coiling explains the positive findings of ISAT for coiling.

Appendix

Participating Centers that responded to the questionnaire (patients):
Nottingham, UK, Queens Medical Centre (272). Oxford, UK, Radcliffe Infirmary (249). Salford, UK, Hope Hospital and Manchester Royal Infirmary (222). Newcastle, UK, Western General Hospital (62) Birmingham, UK, Queen Elizabeth Hospital (60) Bristol, UK, Frenchay Hospital (59) Cardiff, UK, University Hospital of Wales (57) Liverpool, UK, Walton Centre for Neurology and Neurosurgery (54) London, UK, Atkinson Morley Hospital (37) Montréal, Canada, Hôpital Notre Dame (27) Plymouth, UK, Derriford Hospital (25) Odense, Denmark, UniversitetsHospital (25) Belfast, UK, Royal Hospitals (22) Sheffield, UK, Royal Hallamshire Hospital (19) Cambridge, UK, Addenbrookes Hospital (4) London, UK, National Hospital for Neurological Diseases (3) Romford, UK, Oldchurch Hospital (1).

Sources of Funding

The International Subarachnoid Aneurysm Trial is supported by grants from: the Medical Research Council, UK; and Programme Hospitalier de Recherche Clinique 1998 of the French Ministry of Health (AOM 98150). It is sponsored by Assistance Publique, Hôpitaux de Paris (AP-HP); the Canadian Institutes of Health Research; and the Stroke Association of the UK for the Neuropsychological assessments. This study was in part supported by a grant from the Netherlands Heart Foundation (grant 2005 B16).

Disclosures

None.

References

Effect of Antiplatelet Therapy for Endovascular Coiling in Aneurysmal Subarachnoid Hemorrhage

Walter M. van den Bergh, Richard S.C. Kerr, Ale Algra, Gabriel J.E. Rinkel and Andrew J. Molyneux

for the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group

*Stroke*. 2009;40:1969-1972; originally published online April 23, 2009;
doi: 10.1161/STROKEAHA.108.528802

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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/40/6/1969

**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/