Endothelin Receptor Antagonists for Aneurysmal Subarachnoid Hemorrhage
A Systematic Review and Meta-Analysis Update

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Background and Purpose—Endothelin is considered to be a key mediator of vasospasm after subarachnoid hemorrhage. A meta-analysis of randomized trials on the effectiveness of endothelin receptor antagonists in subarachnoid hemorrhage has been published previously, but since then new major trials have been published. We present the results of a systematic review and meta-analysis update.

Methods—We searched the Cochrane Library, the Cochrane Central Register of Controlled Trials, and PubMed with the following terms: subarachnoid hemorrhage AND (endothelin receptor antagonist OR clazosentan OR TAK-044 OR bosentan). All randomized, placebo-controlled trials investigating the effect of any endothelin receptor antagonists in patients with subarachnoid hemorrhage were included. Primary outcome was poor functional outcome (defined as death or dependency). Secondary outcomes were vasospasm, cerebral infarction as defined by investigators, and case fatality during follow-up. Data were pooled and effect sizes were expressed as risk ratio (RR) estimates with 95% confidence intervals (CI). We also calculated RR for several common complications.

Results—In 5 trials with 2601 patients, endothelin receptor antagonists tended to increase the risk of poor functional outcome (RR, 1.12; 95% CI, 0.97–1.28) despite a decreased incidence of angiographic vasospasm (RR, 0.58; 95% CI, 0.48–0.71). No effect was observed on vasospasm-related cerebral infarction (RR, 0.76; 95% CI, 0.53–1.11), any new cerebral infarction (RR, 1.04; 95% CI, 0.91–1.19), or case-fatality (RR, 1.04; 95% CI, 0.78–1.39). Endothelin receptor antagonists increased the risk of lung complications (RR, 1.79; 95% CI, 1.52–2.11), pulmonary edema (RR, 2.12; 95% CI, 1.32–3.39), hypotension (RR, 2.42; 95% CI, 1.78–3.29), and anemia (RR, 1.47; 95% CI 1.19–1.83).

Conclusion—These results argue against the use of endothelin receptor antagonists in patients with subarachnoid hemorrhage. (Stroke. 2012;43:00-00.)

Key Words: antagonist ■ cerebral infarction ■ endothelin receptor ■ delayed cerebral ischemia ■ outcome ■ subarachnoid hemorrhage ■ systematic review ■ vasospasm

Delayed cerebral ischemia is a common and serious complication after aneurysmal subarachnoid hemorrhage (SAH). Delayed cerebral ischemia is sometimes reversible, but it may also progress to cerebral infarction, which increases the risk of severe disability and death after SAH. The pathogenesis of delayed cerebral ischemia remains unknown. It is assumed that vasospasm plays an important role, because it is strongly associated with neurological deterioration and cerebral infarction after SAH.1 The most potent vasoconstrictor known to date, endothelin, is considered to be a key mediator of vasospasm after SAH.2 Several trials have been performed to investigate the efficacy of endothelin receptor antagonists in patients with SAH. A meta-analysis has been published previously,3 but since then 2 major trials have been published.4,5 Here, we present the results of a systematic review and meta-analysis update.

Materials and Methods
For this systematic review, the Cochrane Collaboration format was used.

Definitions
Poor functional outcome was defined as a Glasgow Outcome Scale score of 1 to 3, an extended Glasgow Outcome Scale score of 1 to 4, a modified Rankin Scale score of 4 to 6, or death or dependency if no scale was provided.7

Angiographic vasospasm was defined as a reduction in the cerebral arterial diameter of any cerebral artery of at least 33% on a conventional cerebral angiogram, compared with a previous angiogram. In case a study used a limit of angiographic vasospasm <33%
or no limit at all, or defined vasospasm as increased blood flow velocities on transcranial Doppler examination, these data were not included in the meta-analysis.

Vasospasm-related cerebral infarction was defined as any new hypodensity on follow-up head computed tomography scan compared with a postprocedure computed tomography scan, with vasospasm in the appropriate territory. Any new cerebral infarction was defined as a new or enlarged hypodensity from all causes on follow-up head computed tomography scan compared with a previous computed tomography scan, or recent cerebral infarction at autopsy.

Lung complications, pulmonary edema, hypotension, hepatobiliary events, disorders of cardiac rhythm or conduction, and anemia were not predefined but were included in the meta-analyses for common in-hospital complications if these outcome measures were presented in the included studies.

Selection Criteria: Types of Studies, Participants, and Intervention

All randomized, placebo-controlled trials investigating the effect of endothelin receptor antagonists in patients with aneurysmal SAH were included, regardless of type of drug, dosage used, and follow-up duration.

Types of Outcome Measures

Primary outcome was poor functional outcome. Secondary outcomes were angiographic vasospasm, vasospasm-related cerebral infarction, any new cerebral infarction, and case fatality during follow-up. We also recorded the following common in-hospital complications: lung complications, pulmonary edema, hypotension, hepatobiliary events, disorders of cardiac rhythm or conduction, and anemia.

Search Strategy for Identification of Studies

Two of the authors (M.D.I.V. and G.J.E.R.) systematically searched the PubMed database up to May 28, 2012, using the following terms: subarachnoid hemorrhage AND (endothelin receptor antagonist OR clazosentan OR TAK-044 OR bosentan). The search was limited to studies in humans. Furthermore, we searched for relevant studies in the Cochrane Library and the Cochrane Central Register of Controlled Trials. Citations used in articles that were included in the present review were manually searched for new studies. Actelion Pharmaceuticals was contacted for individual patient data of all CONSCIOUS trials.

Assessment of Risk of Bias in Included Studies

One review author (M.D.I.V.) assessed risk of bias in each included study for the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias.6 In accordance with the Cochrane Collaboration tool for assessing risk of bias, each criterion was rated as either “low risk of bias,” “high risk of bias,” or “unclear risk of bias” (indicating either lack of information or uncertainty over the potential for bias).6 To obtain more information on methodology of the included studies, we also searched the literature for articles describing rationale and design of included studies.

Statistics

If a study did not report on the number of patients using placebo or endothelin receptor antagonist treatment having a certain outcome event, then these numbers were calculated from percentages presented in Tables or Figures. If data could not be retrieved from Tables or Figure as well, then the data could not be included in the meta-analysis. Data were processed in Review Manager 5.1.6 as supplied by the Cochrane Collaboration. Effect sizes were expressed in (pooled) risk ratio (RR) estimates and absolute risk reductions or absolute risk increases (ARI), and numbers needed to treat when applicable. Statistical uncertainty was expressed as 95% confidence intervals (CI). In case the I² statistic showed our data to be heterogeneous (defined as I² >50%), we used a random-effects model. Otherwise, we used a fixed-effects model. When heterogeneity was found on efficacy analysis, we explored heterogeneity by stratifying for trial quality (low risk of bias on all items vs high or unclear risk of bias on any item). For effectiveness outcome measures, we performed subgroup analyses for type of endothelin receptor antagonist used and type of treatment (clipped vs coiled aneurysms).

Results

Our search strategy revealed 48 citations. After reading all abstracts, 5 randomized, placebo-controlled trials were included, describing 2601 patients in total.4,5,8–10 One article was retrieved that provided additional data on the incidence of vasospasm-related infarction in 1 of the included trials.11 Actelion Pharmaceuticals declined to provide individual patient data or data to enable at least intention-to-treat analyses of the CONSCIOUS-2 and CONSCIOUS-3 trials.4,5 Because these trials included the highest numbers of patients of all trials included in this systematic review, no further efforts were undertaken to obtain individual patient data of the other included trials. The characteristics of the included studies are listed in the Table. In 3 trials, the numbers of patients randomized to treatment and placebo were not equal, because it was a dose-finding trial with 3 treatment groups and 1 placebo group,10 a 2:1 randomization,4 or a phase III trial with 2 different dosages in the treatment group.5 In 1 study, analyses were performed on an intention-to-treat basis.8 In other studies, data on efficacy were analyzed in the all-treated set4,5,9,10 or the per-protocol set.10 Because no additional data were provided, we had to pool data of all trials independent of type of analysis.

Assessment of Risk of Bias in Included Studies

One additional article was retrieved that described methodological aspects of 2 included studies.2,4,5 In our risk of bias assessment, we assumed that methodological details of these 2 studies were identical as for another study that was sponsored by the same pharmaceutical company.10 Risk of bias was low in all 5 included studies for the items random sequence generation, selective reporting, and other sources of bias.4,5,8–10 For allocation concealment and blinding, risk of bias was low in 4 studies4,5,8,10 and unclear in 1 study.9 For incomplete outcome data, risk of bias was low in 2 studies,4,9 high in 2 studies,5,8 and unclear in 1 study.10

Analyses: Primary Outcome

For the analysis of poor functional outcome, data from four studies including 2551 patients were available (1676 patients received treatment with an endothelin receptor antagonist and 875 patients received placebo).4,5,8,10 Data on poor functional outcome were based on an intention-to-treat analysis in 1 trial4 and an on-treatment analysis in 3 trials.4,5,10 Poor functional outcome was defined as a Glasgow Outcome Scale of 1 to 3 in 1 study4 and as an extended Glasgow Outcome Scale of 1 to 4 in 3 studies.4,5,10 In all 4 studies, functional outcome was assessed 3 months after SAH.4,5,8,10 For poor functional outcome, the pooled RR was 1.12 (95% CI, 0.97–1.28) and the ARI was 3% (95% CI, –1% to 7%; Figure 1). Data on poor outcome did not indicate heterogeneity (I²=0%).
Secondary Outcomes
For the analysis of the proportion of patients with angiographic vasospasm, data from 2 studies including 441 patients were available (328 patients received treatment with an endothelin receptor antagonist and 113 patients received placebo).9,10 To investigate the presence of angiographic vasospasm, digital subtraction angiography was performed on day 8 to 11 after aneurysm rupture in 1 study9 and on day 9 to 10 in the other trial.10 In 1 trial, data on angiographic vasospasm were available for 32 of the 34 randomized patients.9 In 2 other patients, angiographic vasospasm could not be assessed because of death. In the other trial that presented data on angiographic vasospasm, data were available for 409 of the 413 patients.10 Because this was a dose-finding trial to identify the safest and most effective dose of clazosentan for prevention of angiographic vasospasm, no intention-to-treat analysis was performed; but an all-treated analysis, excluding 4 patients who did not receive study medication, was performed. 

Table. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N of Randomized Patients</th>
<th>Type and Duration of Treatment</th>
<th>Age Eligibility (y)</th>
<th>Definition of Vasospasm</th>
<th>Definition of Cerebral Infarction</th>
<th>Time of Functional Outcome Assessment</th>
<th>Type of Functional Outcome Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaw et al (2000)</td>
<td>420</td>
<td>TAK-044 150 mg 3 times per day (initial 3-step [10, 25, 50 mg] dose-escalation period, followed by a maintenance period on the maximum tolerated dose), during 10 d</td>
<td>18 or older</td>
<td>Not an outcome</td>
<td>Cerebral infarct visualized on a CT scan or at autopsy during the 3 mo after SAH</td>
<td>3 mo</td>
<td>GOS</td>
</tr>
<tr>
<td>Vajkoczy et al (2005)</td>
<td>34</td>
<td>Clazosentan 0.2 mg/kg/hour, for up to 14 d after SAH</td>
<td>18 to 65</td>
<td>A reduction in the arterial diameter &gt;33% compared with vessel diameter on the preoperative angiogram</td>
<td>New hypodensities on CT scan 14 d after SAH, compared with the preoperative CT scan</td>
<td>14 d</td>
<td>GOS</td>
</tr>
<tr>
<td>Macdonald et al (2008)</td>
<td>413</td>
<td>Clazosentan 1 mg/hour, 5 mg/hour, or 15 mg/hour, during 14 d</td>
<td>18 to 70</td>
<td>A reduction in the arterial diameter &gt;33% between baseline and digital subtraction angiogram 9 ± 2 d after SAH</td>
<td>New cerebral infarct attributable to vasospasm within 6 wk of SAH, compared with postprocedure CT scan</td>
<td>12 wk</td>
<td>Extended GOS</td>
</tr>
<tr>
<td>Macdonald et al (2011)</td>
<td>1157</td>
<td>Clazosentan 5 mg/hour, for up to 14 d after SAH</td>
<td>18 to 75</td>
<td>Not an outcome</td>
<td>New cerebral infarct within 6 wk of SAH for which vasospasm was the primary cause or a relevant contributing factor</td>
<td>12 wk</td>
<td>Extended GOS</td>
</tr>
<tr>
<td>Macdonald et al (2012)</td>
<td>577</td>
<td>Clazosentan 5 mg/hour, or 15 mg/hour, for up to 14 d after SAH</td>
<td>18 to 75</td>
<td>Not an outcome</td>
<td>New cerebral infarct within 6 wk of SAH for which vasospasm was the primary cause or a relevant contributing factor</td>
<td>12 wk</td>
<td>Extended GOS</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; GOS, Glasgow Outcome Scale; SAH, subarachnoid hemorrhage.

Figure 1. Pooled relative risk estimates for patients using endothelin receptor antagonists to have poor functional outcome.
formed. Endothelin receptor antagonists decreased the incidence of angiographic vasospasm (pooled RR, 0.58; 95% CI, 0.48–0.71; absolute risk reduction −29%; 95% CI, −39% to −18%; Figure 2). Data in the vasospasm meta-analysis did not indicate heterogeneity (I²=0%).

For the analysis of the occurrence of vasospasm-related cerebral infarction, data of 3 studies including 2127 patients were available (1459 patients received treatment with an endothelin receptor antagonist and 668 patients placebo). Endothelin receptor antagonists did not decrease the incidence of vasospasm-related cerebral infarction (pooled RR, 0.76; 95% CI, 0.53–1.11; absolute risk reduction, −3%; 95% CI, −7% to 1%; Figure 3). Data in the vasospasm-related cerebral infarction meta-analysis demonstrated heterogeneity (I²=53%).

For the analysis of the occurrence of any new cerebral infarction, data of 3 studies including 1596 patients were available (984 patients received treatment with an endothelin receptor antagonist and 612 patients placebo). Endothelin receptor antagonists did not affect the incidence of any new cerebral infarction (pooled RR, 1.04; 95% CI, 0.91–1.19; ARI, 2%; 95% CI, −3% to 6%; Figure 4). Data in the meta-analysis including any new cerebral infarction did not indicate heterogeneity (I²=25%).

All 5 studies analyzed case fatality. For this analysis, data from 2591 patients were available (1686 patients received treatment with an endothelin receptor antagonist and 905 patients received placebo). Data on case fatality were based on an intention-to-treat analysis in 2 trials and an on-treatment analysis in 3 trials. For case fatality, the pooled RR was 1.04 (95% CI, 0.78–1.39) and the absolute risk reduction was 0% (95% CI, −2% to 2%; Figure 5). Data on case fatality did not indicate heterogeneity (I²=0%).

### Complications

Data on complications were based on an intention-to-treat analysis in 1 trial and an on-treatment analysis in 3 trials whereas this was unclear in 1 trial. Endothelin receptor antagonists increased the risk of lung complications (4 studies with 2161 patients: RR, 1.79; 95% CI, 1.52–2.11; ARI, 16%; 95% CI, 12%–20%). Pulmonary edema (3 studies with 2127 patients: RR, 2.14; 95% CI, 1.57–2.92; ARI, 8%; 95% CI, 5%–10%) and hypotension (4 studies with 2547 patients: RR, 2.42; 95% CI, 1.78–3.29; ARI, 8%; 95% CI, 5%–10%) and anemia (3 studies with 2127 patients: RR, 1.47; 95% CI, 1.19–1.83; ARI, 6%; 95% CI, 3%–10%). No effect was found for hepatobiliary events (3 studies with 1752 patients: RR, 1.10; 95% CI, 0.89–1.36; ARI, 2%; 95% CI, −2% to 6%) or disorders of cardiac rhythm or conduction (2 studies with 1718 patients: RR, 1.05; 95% CI, 0.61–1.82; ARI, 1%; 95% CI, −5% to 6%). Heterogeneity was only observed in the meta-analysis of disorders of cardiac rhythm or conduction (I²=68%), but not in other complication-related meta-analyses.

### Subgroup and Sensitivity Analyses

A subgroup analysis was performed for type of endothelin receptor antagonist used. One study randomized 420 patients to either TAK-044 or placebo, and 4 studies had a total 2181 of patients randomized to either clazosentan or placebo. For the outcome measures poor functional outcome, any new cerebral infarction, and case fatality, tests for heterogeneity of results between subgroups indicated no differences (all I²=0%; Figures 1, 4, 5).

Another subgroup analysis was performed for type of aneurysm treatment. Two studies investigated the effectiveness of endothelin receptor antagonists in patients who had their aneurysm clipped and 1 study investigated the effectiveness of endothelin receptor antagonists in patients who had their aneurysm coiled. Data on functional outcome were reported in 2 trials and data on case fatality were reported in 3 trials. For patients who had their aneurysm clipped, the pooled RR was 1.18 (95% CI, 0.96–1.45), and for those who had their aneurysm coiled the RR was 1.12 (95% CI, 0.83–1.52). Test for heterogeneity of results between subgroups indicated no differences (I²=0%). No effect on case fatality was observed in patients with clipped and coiled aneurysms (RR, 1.02; 95% CI, 0.64–1.64; and RR, 0.93; 95% CI, 0.42–2.06), respectively. Test for heterogeneity of results between subgroups indicated no differences (I²=0%).

A sensitivity analysis was performed for the outcome measure vasospasm-related cerebral infarction, because heterogeneity was observed in that analysis. Of the 3 included studies, risk of bias was low for all items in 1 study, high for 1 item in 1 study, and unclear for 1 item in another study. After exclusion of the 2 studies with high and unclear risk of
bias, only 1 trial was available for analysis in which no effect was observed on vasospasm-related cerebral infarction (RR, 0.92; 95% CI, 0.67–1.27). Because only 1 trial was available for analysis, heterogeneity could no longer be explored.

### Discussion

The results of this systematic review show that endothelin receptor antagonists tend to increase the risk of poor functional outcome after SAH, despite a beneficial effect on angiographic vasospasm. Endothelin receptor antagonists do not affect the incidence of vasospasm-related cerebral infarction, any new cerebral infarction, or case fatality. Subgroup analyses for type of endothelin receptor antagonist and type of aneurysm treatment showed no differences between subgroups.

Our results are in line with a previous systematic review on the efficacy of endothelin receptor antagonists in patients with SAH. However, the previous systematic review only included data from 3 studies with 867 patients. We added data of 2 recent studies with another 1734 patients. Therefore, our review has more power to detect a potential effect on all outcome measures. Moreover, in contrast to the previous meta-analysis, we performed several subgroup analyses.

We found that use of endothelin receptor antagonists does not improve functional outcome after SAH, but we also noted a trend toward a higher risk of poor functional outcome in patients treated with endothelin receptor antagonists, which may be explained by an increased incidence of lung complications, pulmonary edema, hypotension, and anemia. These complications have been associated with worse functional outcomes in previous studies. The lack of effect on functional outcome of endothelin receptor antagonists also can be explained by a lack of effect on the incidence of both vasospasm-related infarctions and any new cerebral infarctions. Whereas there is general consensus that vasospasm is associated with neurological deterioration, cerebral infarction, poor functional outcome, and case fatality after SAH, causal relationships are subject to discussion. Our findings suggest that the pathogenesis of cerebral infarctions from delayed cerebral ischemia is multifactorial and confirm previous observations that a lower incidence of angiographic vasospasm does not correspond with better functional outcomes. Besides vasospasm, additional pathophysiological mechanisms are likely involved, such as cortical spreading ischemia/depression, microthrombosis, and disturbed autoregulation. Because of this multifactorial pathogenesis, the prevention of angiographic vasospasm is not sufficient to decrease the incidence of vasospasm-related cerebral infarctions.

The strength of this meta-analysis is that we used a common and widely accepted primary outcome measure, namely poor functional outcome defined as death or dependency.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Total</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>4.1.1 TAK-044</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shaw 2000</td>
<td>32</td>
<td>207</td>
<td>33</td>
<td>213</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>32</td>
<td>207</td>
<td>33</td>
<td>213</td>
</tr>
<tr>
<td>Total events</td>
<td>64</td>
<td>404</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 0.01 (P = 0.99)</td>
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<td></td>
<td></td>
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<tr>
<td>4.1.2 Cilazapril</td>
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<tr>
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<td>20</td>
<td>131</td>
<td>4</td>
<td>96</td>
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<td>Macdonald 2011</td>
<td>44</td>
<td>768</td>
<td>22</td>
<td>389</td>
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<tr>
<td>Macdonald 2012</td>
<td>17</td>
<td>382</td>
<td>9</td>
<td>169</td>
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<tr>
<td>Valjacić 2005</td>
<td>3</td>
<td>16</td>
<td>3</td>
<td>13</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>1479</td>
<td>692</td>
<td>60.7%</td>
<td>1.06 [0.73, 1.55]</td>
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<tr>
<td>Total events</td>
<td>64</td>
<td>404</td>
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<tr>
<td>Heterogeneity: CH² = 0.61, df = 3 (P = 0.89); I² = 0%</td>
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<td>Test for overall effect: Z = 0.32 (P = 0.75)</td>
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<tr>
<td>Total (95% CI)</td>
<td>1686</td>
<td>905</td>
<td>100.0%</td>
<td>1.04 [0.78, 1.39]</td>
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<tr>
<td>Total events</td>
<td>116</td>
<td>71</td>
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<tr>
<td>Heterogeneity: CH² = 0.65, df = 4 (P = 0.96); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 0.26 (P = 0.80)</td>
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<tr>
<td>Test for subgroup differences: CH² = 0.05, df = 1 (P = 0.83); I² = 0%</td>
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</table>

Figure 4. Pooled relative risk estimates for patients using endothelin receptor antagonists to have any new cerebral infarction.

Figure 5. Pooled relative risk estimates of case fatality for patients using endothelin receptor antagonists.
dency. Many of the included studies used a combined morbidity/mortality end point (defined as all cause-mortality, vasospasm-related new cerebral infarcts, delayed ischemic neurological deficit attributable to vasospasm, and rescue therapy for vasospasm), which made them more difficult to interpret.4,5,10 Furthermore, this meta-analysis included data of several randomized trials with 2601 patients, and it hereby provides the highest level of evidence that endothelin receptor antagonists are not effective in patients with SAH. We also showed in a subgroup analysis that these drugs are not effective in patients with clipped aneurysms or in those with coiled aneurysms. Another subgroup analysis showed a lack of efficacy of both TAK-044 and clazosentan. Some limitations need to be addressed. First, no definitions were given for common in-hospital complications because the included studies did not provide these definitions. Second, we did not use a recently described definition for cerebral infarction that was proposed by consensus of an international panel of SAH investigators.3,5 We decided not to use that definition for this review because the included studies used other definitions. Third, in all included studies, pharmaceutical companies were involved. In at least 3 of the included trials, data collection and statistical analyses were performed by the pharmaceutical company that funded the trial.4,5,10 We were not given individual patient data of all patients, so we were unable to perform more subgroup analyses to investigate efficacy of endothelin receptor antagonists in these subgroups. Lack of providing additional data also hampered the analysis for the most relevant clinical outcome measure, namely poor functional outcome, because only 2 trials performed an intention-to-treat analysis.8,9 Finally, we had ethical concerns on performing digital subtraction angiographies for study purposes in 2 of the included trials, because these diagnostic tests have a complication risk.9,10

Our results have implications for clinical practice, namely that endothelin receptor antagonists should not be administered to patients with SAH, given the lack of effectiveness and the increased risk of complications. Implications for research are that individual patient data should be analyzed to explore if there are subgroups for which endothelin receptor antagonists might be effective.

Disclosures

None.

References


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