Patients with an aneurysmal subarachnoid hemorrhage (SAH) still have a poor prognosis: around a third of patients die within the first month.1 Delayed cerebral ischemia (DCI) is an important contributor to the poor outcome after SAH.2,3 DCI does usually not occur before day 3 or 4 after the SAH, and so in theory there is a time window to start with neuroprotective therapy after the hemorrhage but before the occurrence of DCI.2 However, in a meta-analysis of all trials on magnesium therapy in SAH no effect on clinical outcome was found.4 An explanation for the lack of a beneficial effect of magnesium might be that the study medication was started too late. In all trials on magnesium therapy in SAH, study medication could be started late, ≤4 days after the SAH. For example, in Magnesium in Subarachnoid Hemorrhage (MASH)-II, the largest study, the median time between the SAH and start of study drug was 37 hours.4 We hypothesized that the cascade leading to DCI already begins very early after the SAH, and that earlier installment of treatment might be more effective, but individual trials had not enough power for such a subanalysis. We performed an individual patient data meta-analysis to study whether magnesium is effective when given within different time frames within 24 hours after the SAH.

Methods—Patients were divided into categories according to the delay between symptom onset and start of the study medication: <6, 6 to 12, 12 to 24, and >24 hours. We calculated adjusted risk ratios with corresponding 95% confidence intervals for magnesium versus placebo treatment for poor outcome and DCI.

Results—We included 5 trials totaling 1981 patients; 83 patients started treatment <6 hours. For poor outcome, the adjusted risk ratios of magnesium treatment for start <6 hours were 1.44 (95% confidence interval, 0.83–2.51); for 6 to 12 hours 1.03 (0.65–1.63), for 12 to 24 hours 0.84 (0.65–1.09), and for >24 hours 1.06 (0.87–1.31), and for DCI, <6 hours 1.76 (0.68–4.58), for 6 to 12 hours 2.09 (0.99–4.39), for 12 to 24 hours 0.80 (0.56–1.16), and for >24 hours 1.08 (0.88–1.32).

Conclusions—This meta-analysis suggests no beneficial effect of magnesium treatment on poor outcome or DCI when started early after SAH onset. Although the number of patients was small and a beneficial effect cannot be definitively excluded, we found no justification for a new trial with early magnesium treatment after SAH. (Stroke. 2015;46:3190-3193. DOI: 10.1161/STROKEAHA.115.010575.)

Key Words: brain ischemia ■ magnesium ■ meta-analysis ■ stroke ■ subarachnoid hemorrhage

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*A list of all writing group members is given in the Appendix.

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Methods

Trials that studied magnesium sulfate versus placebo in SAH patients were identified from our updated Cochrane meta-analysis that was performed as part of our publication of the MASH-II study in 2012, supplemented with a new PubMed search (search terms: magnesium, subarachnoid hemorrhage) performed for articles that were published in 2012 until December 2014. Also, we contacted the principal investigators of a large trial that was being conducted at the time, studying prehospital magnesium therapy in stroke patients, and asked them whether any aneurysmal subarachnoid hemorrhage (aSAH) patients were included. We contacted all other principal investigators of the identified trials for participation in this meta-analysis. To participate, they should be able to provide at least the treatment allocation, clinical outcome between 3 and 6 months, age, sex, clinical condition on admission (with the World Federation of Neurological Surgeons score, WFNS), and time interval between SAH and start of study treatment. Data on occurrence of DCI were encouraged but not mandatory. A WFNS score of 4 to 5 was considered a poor clinical condition on admission.

The primary outcome measure was poor clinical outcome, defined as death or dependency at 3 to 6 months (a modified Rankin Scale score of 4–5 or death, a Glasgow Outcome Scale score of 1–3). The secondary outcome was DCI, where definition was left to the individual researchers of the included trials.

We categorized the included patients according to the time interval between the SAH and the start of the study drug as follows: within 6 hours, between 6 and 12 hours, between 12 and 24 hours, and later than 24 hours. If timing was not exactly known, because point of time of the SAH ictus was not known, we used the point of time when the patient was last seen well. With this approach, we assured that patients in the timing category <6 hours were really treated within 6 hours. For patients in later timing categories, some patients could actually have been treated earlier, but never later.

We performed analyses for poor outcome and DCI for each timing category and for all patients treated within 24 hours. We calculated risk ratios with 95% confidence intervals for poor outcome and DCI for magnesium versus placebo with Poisson regression analysis. Risk ratios were adjusted for age, sex, and clinical condition on admission.

All studies included in the review had ethical approval.

Results

Besides the 7 trials in the meta-analysis of 2012, 2 new trials were identified (including the trial aimed at stroke patients). Data were provided for 5 trials: MASH-I (Utrecht, The Netherlands), the international MASH-II, Intravenous Magnesium in Subarachnoid Hemorrhage (IMASH; Hong-Kong, China), MASH (Sydney, Australia), and Field Administration of Stroke Therapy – Magnesium (FAST-MAG; Los Angeles, CA; Figure 1). The aSAH trials ranged in size from 162 to 1204 patients. The stroke trial included 1700 patients in total, from whom 5 patients had an aSAH, who were included in this study. Treatment regimens differed slightly between the trials (Table 1). Description of DCI varied between the included trials; 1 used computed tomography hypodensities in combination

### Table 1. Characteristics of Included Trials

<table>
<thead>
<tr>
<th>N (Magnesium/Placebo)</th>
<th>Dose/Route Study Drug Administration</th>
<th>DCI/Vasospasm</th>
<th>Outcome (Timing of Assessment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MASH-I²</td>
<td>Continuous IV 64 mmol/L per day</td>
<td>Occurrence of new spontaneous hypodense lesion on CT compatible with clinical features of DCI</td>
<td>mRankin (3 mo)</td>
</tr>
<tr>
<td>IMASH³</td>
<td>20 mmol IV in 30 min, followed by continuous IV 80 mmol/d, dose adjusted until twice the baseline value and &lt;2.5 mmol/L</td>
<td>New focal neurological deficits or decrease in the Glasgow Coma Scale score of &gt;2 points for &gt;6 h or new cerebral infarction not otherwise explained</td>
<td>mRankin, GOS-E (6 mo)</td>
</tr>
<tr>
<td>MASH-II⁴</td>
<td>Continuous IV 64 mmol/L per day</td>
<td>Clinically: new focal neurological deficits or decrease in the Glasgow Coma Scale score of &gt;2 points for &gt;6 h or new cerebral infarction not otherwise explained†</td>
<td>mRankin (3 mo)</td>
</tr>
<tr>
<td>MASH⁵</td>
<td>Continuous intravenous, dosage titrated until serum magnesium between 1.6 and 2.5 mmol/L</td>
<td>Cerebral arterial vasospasm on digital subtraction angiography</td>
<td>mRankin and GOS (3 mo)</td>
</tr>
<tr>
<td>FAST-MAG⁶</td>
<td>15-min bolus infusion of 4 g, followed by 24 h continuous infusion of 16 g over 24 h</td>
<td>No information</td>
<td>mRankin (3 mo)</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; DCI, delayed cerebral ischemia; FAST-MAG, Field Administration of Stroke Therapy – Magnesium; GOS-E, Extended Glasgow Outcome Scale; IMASH, Intravenous Magnesium in Subarachnoid Hemorrhage; and MASH, Magnesium in Subarachnoid Hemorrhage.

*In 1 patient, randomization code missing.
†Left to discretion of treating physician.
with clinical features suspect of DCI, 9, 10 used a definition of either computed tomography infarction or clinical signs, 4, 10 one study used angiographic vasospasm without a clinical definition as outcome measurement, 4 and in one study no information was available on DCI. 6 Because angiographic vasospasm is different from the other definitions of DCI, we decided not to include the patients of this trial in the analysis for DCI.

The 5 included trials totaled 1981 patients, 997 received magnesium therapy and 983 placebo, in 1 patient the randomization code was lost. We had to exclude 10 patients because time between SAH and start of study medication could not be established. For the analysis of poor outcome, 5 more patients were excluded because outcome was unknown, leaving 1965 patients for analysis. Because the patients of 2 trials were not included for DCI analysis, 1804 patients were available for the analysis of DCI. Baseline characteristics of the patients in the different timing groups are shown in Table 2.

In none of the timing groups, the adjusted risk ratio of magnesium treatment showed a statistically significant effect or trend toward good outcome (Figure 2). Also for DCI, in none of the timing groups, we saw a statistically significant effect of magnesium treatment toward less DCI (Figure 3).

Discussion

In this individual patient data meta-analysis of randomized clinical trials on magnesium treatment in SAH, we found no beneficial effect on poor outcome or DCI in patients who were treated within 6, between 6 and 12, or between 12 and 24 hours after the SAH.

There were only 83 patients who were treated within 6 hours, making the estimates for poor outcome and DCI in this time window imprecise. Although no definite conclusions can be drawn, in this small subgroup not even a hint toward a beneficial effect was found.

We also included 5 patients of the FAST-MAG trial that was not aimed at aSAH patients but at stroke patients with deficits in general (ischemic and hemorrhagic stroke) and studied early, prehospital administration of magnesium. 6 The trial totaled 1700 stroke patients and trial medication was started within a median time of 45 minutes after the ictus, and no effect on outcome was shown. This is in line with our negative result of early magnesium administration in patients with SAH.

Strong points of our study are that with an individual data meta-analysis, we were able to create subgroups according to timing that could not be assessed in the original trials, because of too small numbers per subgroup in the original studies. The trials were similar with regard to treatment schedule, inclusion and randomization of patients, outcome measures, and outcome results. If the exact timing of the SAH was unknown, we used the last seen well-time to calculate the time between SAH and start of study treatment, to assure that patients in the <6 hours timing category were really treated within this time frame. The main weakness is that even in this meta-analysis, we found that only 83 of 1981 patients were treated within 6 hours. Apparently, early inclusion is difficult, for example, because of delays in reaching the hospital or admittance during the night when the informed consent procedure was postponed until the next day. Another weak point might be that we could not include data of 4 trials, because the principal

### Table 2. Baseline Characteristics of Included Patients in Different Timing Categories and According to Study Treatment

<table>
<thead>
<tr>
<th></th>
<th>≤ 6h</th>
<th>6–12 h</th>
<th>12–24 h</th>
<th>&gt;24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mg</strong></td>
<td>n=44</td>
<td>Placebo, n=39</td>
<td>n=96</td>
<td>Placebo, n=77</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>57 (14)</td>
<td>56 (9)</td>
<td>55 (13)</td>
<td>58 (13)</td>
</tr>
<tr>
<td>Female sex</td>
<td>28 (64%)</td>
<td>28 (72%)</td>
<td>63 (66%)</td>
<td>56 (73%)</td>
</tr>
<tr>
<td>Poor clinical condition</td>
<td>11 (25%)</td>
<td>13 (33%)</td>
<td>20 (21%)</td>
<td>14 (18%)</td>
</tr>
</tbody>
</table>

Figure 2. Adjusted risk ratio (RR) for poor outcome for magnesium versus placebo, according to timing category. CI indicates confidence interval.

Figure 3. Adjusted risk ratio (RR) for occurrence of delayed cerebral ischemia (DCI) for magnesium versus placebo, according to timing category. CI indicates confidence interval.
investigators did not respond to our request. However, these were all small studies and totaled only 237 patients and they did not aim at early study treatment, so we do not expect that this has substantially influenced our results.

In conclusion, our data show no beneficial effect of magnesium treatment in SAH and do not justify a trial studying early magnesium treatment in patients with SAH.

Appendix

Collaborators (divided per study group, for full study groups see original publications)Members of the MASH-I writing groupW.M. van den Bergh, MD, PhD (University Medical Center Utrecht, project coordinator); A. Algra (University Medical Center Utrecht, Utrecht); F. van Kooten, MD, PhD (Erasmus Medical Center, site investigator); C.M. Dirven, MD, PhD (VU University Medical Center, site investigator); J. van Gijn, MD, PhD (University Medical Center Utrecht, site investigator); M. Vermeulen, MD, PhD (Academic Medical Center, site investigator); G.J.E. Rinkel, MD, PhD (University Medical Center Utrecht, study supervisor). This trial was funded by the Netherlands Heart Foundation (grant no. 99.107). Members of the IMASH writing groupW.S. Poon (Prince of Wales Hospital, site investigator); G.K.C. Wong, MD, PhD (Prince of Wales Hospital, study supervisor); R. Boet, MD, PhD (Prince of Wales Hospital, site investigator); M.T.V. Chan, MD (Prince of Wales Hospital, site investigator); T. Gin, MD (Prince of Wales Hospital, site investigator); S.C.P. Ng, MD (Prince of Wales Hospital, site investigator); B.C.Y. Zee, MD (Prince of Wales Hospital, site investigator). This study was supported by the Research Grants Council of Hong Kong (CUHK Ref. No. MASH-II CUHK4183/02 M). Members of the MASH-II writing groupM. Dorhout Mees, MD, PhD (University Medical Center Utrecht, study coordinator); W.M. van den Bergh, MD, PhD (University Medical Center Utrecht, study supervisor); G.J.E. Rinkel, MD (University Medical Center Utrecht, site investigator); A. Algra, MD, PhD (University Medical Center Utrecht, site investigator), R. Al-Shahi Salman, MD, PhD (Western General Hospital, site investigator), J. Boiten, MD, PhD (Medical Center Haaglanden, site investigator), F. van Kooten, MD, PhD (Erasmus Medical Center Rotterdam, site investigator), H. Kuijsten, MD (St Elisabeth Hospital, site investigator), P.M. Lavados, MD, PhD (Universidad de Chile and Clinica Alemana, site investigator), R.J. van Oostenbrugge, MD, PhD (Maastricht University Medical Center, site investigator), W.P. Vandertop, MD, PhD (Academic Medical Center and VU University Medical Center, site investigator). This trial was funded by the Netherlands Heart Foundation (grant no. 2005BO16) and UK Medical Research Council (clinician scientist fellowship G108/613). Members of the MASH writing groupC.M. Bradford (Royal North Shore Hospital, site investigator); S. Finfer (George Institute for Global Health, site investigator); A. O’Connor (Royal North Shore Hospital, site investigator); E. Yarad (Royal North Shore Hospital, site investigator); R. Firth (Royal North Shore Hospital, site investigator); R. McCallister (Royal Hobart Hospital, site investigator); T. Harrington (Royal North Shore Hospital, site investigator); B. Steinfort (Royal North Shore Hospital, site investigator); K. Faulder (Royal North Shore Hospital, site investigator); N. Assaad (Macquarie University Hospital, site investigator); M. Morgan (Macquarie University Hospital, site investigator). This trial was funded by The Brain Foundation Members of the FAST-MAG writing groupJ. Saver, MD, PhD (UCLA, study supervisor); S. Starkman, MD (UCLA, study supervisor); M. Eckstein, MD (Keck School of Medicine, site investigator); S.J. Stratton, MD (UCLA, site investigator); F.D. Pratt, (UCLA, site investigator); S. Hamilton, MD (Stanford University, site investigator); R. Conwit (National Institute of Neurological Disorders and Stroke, site investigator); D.S. Liebeskind (UCLA, site investigator); G Sung. (Keck School of Medicine, site investigator); L Kramer. (Presbyterian Intercommunity Hospital, site investigator); G. Moreau, MD (Long Beach Memorial Medical Center, site investigator); R. Goldweber, MD (Huntington Memorial Hospital, site investigator); N. Sanossian (Keck School of Medicine, site investigator). This trial was supported by the National Institute of Neurological Disorders and Stroke.

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Disclosures

Dr Saver reports an institutional conflict of interest: “The National Institutes of Health provided a research grant for the FAST-MAG trial to the University of California.” The other authors report no conflicts.

References

Early Magnesium Treatment After Aneurysmal Subarachnoid Hemorrhage: Individual Patient Data Meta-Analysis
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