Response to Letter by Chan et al

Response:
Chan and others argue that our analysis in the Magnesium and Acetylsalicylic acid in Subarachnoid Hemorrhage (MASH) study are incomplete because we didn’t report details on the interaction effect between both therapeutic interventions in this trial with a factorial design.1,2

Randomized controlled trials provide the best quality evidence in medical research, but they require a large commitment of time and effort and are therefore expensive. For these reasons, investigators may consider evaluating more than one intervention in the same study. Factorial designs are a highly efficient means to study the effects of multiple treatments by means of randomized trials. In essence, this approach allows 2 questions to be simultaneously answered for little more than the effort of one.

The most powerful analysis of a factorial trial is performed when the efficacy of intervention A is determined by comparing outcomes among all patients treated with A with those of all patients not treated with A, and the efficacy of intervention B by comparing outcomes among all patients treated with B with those of all patients not treated with B. By performing such analyses evidence can be obtained about efficacy from far fewer patients than would be needed if A and B were individually tested in 2 separate trials. This is the analysis performed in the MASH study.

Factorial trials are ideal when the 2 treatments act independently (A is equally effective whether or not the patient is receiving B, and vice versa). In this case, they will show additive effects when used together, and the above mentioned analyses are appropriate. However, in the presence of interactions, the efficacy of A must be determined by comparing outcomes in patients who receive only A with those in patients who receive neither drug, similar for the efficacy of B.

Chan and others refer to a method proposed by McAllister et al to determine the individual effects of each treatment as well as how the treatments might interact with each other.3 This method to generate an “interaction ratio” that compares the effect of each treatment in the presence and absence of the other treatment are equivalent to an examination for heterogeneity in a meta-analysis. Interaction ratios above 1.0 indicate synergy, and interaction ratios below 1.0 indicate antagonism. Interaction ratios of 1.25 or greater and 0.8 or less indicate synergy, and interaction ratios below 1.0 indicate antagonism.

The results of the MASH study are published in Stroke: two separate articles report the effect of magnesium and aspirin, respectively. With the use of the combined data, summarized in Table 1, we can now calculate the interaction ratio according to the method of McAllister et al. The results are shown in Table 2. The interaction ratios for both outcome measurements delayed cerebral ischemia, and poor outcomes are within the normal range of 0.8 to 1.25. The conclusion is that there is no interaction between magnesium and aspirin.

However, it must be noticed that patients eligible for participation in the aspirin versus placebo study differ from the patients eligible for participation in the magnesium versus placebo study in the sense that they survived the critical days toward operation and the procedure itself.

Disclosures
None.

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**TABLE 1. Event Rates in the MASH Trial**

<table>
<thead>
<tr>
<th>Treatment Intervention and Analyses</th>
<th>RRR</th>
<th>Interaction Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium vs true placebo</td>
<td>35%</td>
<td>1.06</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2. Calculation of Relative Risk Reductions and Interaction Ratios From Data in Table 1**

<table>
<thead>
<tr>
<th>Outcome Measurement</th>
<th>Treatment Intervention and Analyses</th>
<th>RRR</th>
<th>Interaction Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed cerebral ischemia</td>
<td>Magnesium vs true placebo</td>
<td>27%</td>
<td>0.82</td>
</tr>
<tr>
<td>Poor outcome</td>
<td>Magnesium vs true placebo</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

RRR indicates relative risk reductions.
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Walter M. van den Bergh
on behalf of the MASH study group

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