CORRESPONDENCE

Secondary Stroke Prevention: Recent Advances

by Prof. Dr. med. Hans-Christoph Diener, Martin Grond, Michael Böhm, Hans-Henning Eckstein, Michael Forsting, in volume 44/2007

Inconsistencies

The literature cited by Professor Diener needs to be looked at in greater detail.

The PROGRESS study – 14% of patients were a priori not evaluated because they did not tolerate the ACE inhibitor perindopril that was used – was based on a definition of hypertension as blood pressure (BP) > 160/90 mm Hg. It is not clear to me how from this, a therapeutic recommendation for hypertension patients is deduced according to the definition of BP > 140/90 mm Hg.

The MOSES study compared a sartan with nitrendipine – a substance that has not been shown to lower mortality in hypertension patients. In spite of this, the number of deaths in the study was numerically higher in patients taking eprosartan. Further, nitrendipine was given at too low a dosage in the study. Claiming class effects of the sartans that exceed mere blood pressure lowering is incorrect.

Especially the cited LIFE study shows a different extent of blood pressure lowering, which is crucial for the stroke risk. Blood pressure normalized in 49% of patients receiving losartan, but in only 46% receiving atenolol.

In the SPARCL study, 1.9% fewer patients had a stroke while being treated with the maximum dosage of atorvastatin. None of my stroke patients would be willing to take atorvastatin as an additional medication if the NNT was 52 over 5 years.

The dipyrimidole studies ESPS2 and ESPRIT, which the author mentions, are based on a comparison with underdosed acetylsalicylic acid. In the meta-analysis of the Antithrombotic Trialists' Collaboration, it clearly says that ASA dosages between 75 mg and 150 mg were investigated – the value of lower dosages remained unclear.

I fear that these inconsistencies may be a pointer to a conflict of interests in the reporting.

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Conflict of interest statement

The author declares a possible conflict of interest in that he is personally financially liable for excess costs if he exceeds the medication budget set by the National Association of Statutory Health Insurance Physicians. He declares no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

Subtherapeutic Dosage

The authors do not mention that in ESPRIT – in the comparison between dipyrimidole+ASA versus ASA – a substantial proportion of patients did not receive sufficiently high doses of ASA (<75 mg/day). It is correct to state that in case of subtherapeutic ASA dosage, additional dipyrimidole offers protection from serious events, with an NNT of 80 per year. This statement is far removed from clinical practice and does not benefit patients, and the NNT is not impressive either.

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B Vitamins and Cerebral Ischemia

Diener et al., in their review of secondary prophylaxis of stroke, propose that four randomized studies have shown unequivocally that combination therapy with vitamins B6, B12, and folic acid is not suitable for the prevention of cerebral ischemias. A closer look at the cited studies yields interesting considerations and gives a different impression.

The VISP study was critically re-analyzed by the authors. After accounting for vitamin B12 malabsorption as the logical cause of the ineffectiveness of folic acid, the results were corrected and the relative risk for cerebral ischemia in this high-risk cohort was lowered by 18% by administration of vitamins (1).

The HOPE study also showed the effectiveness of homocysteine lowering vitamins in secondary prevention, demonstrating a 24% lower relative risk of cerebral ischemia ($p = 0.03$). It remains incomprehensible that the authors rate their only significant study result as incidental and irrelevant. The relevant figure was presented only as an appendix in the electronic version of the study (<http://content.nejm.org/cgi/data/NEJMoa060900/DC1/1>), but not in the printed version (2).

The new analysis of the NORVIT data by independent statisticians has shown favorable effects for the administration of vitamins for all clinical end points (3).

Necessary questions about the duration of treatment, dosages, and drug interactions were not considered in the studies mentioned.

The participants to benefit most are those with raised homocysteine levels and 36 months duration of therapy, which already points to the necessity of target group selection and sufficiently long treatment duration. Most participants in VISP, HOPE, and NORVIT did not have relevant vitamin deficiencies that justified treatment primarily, and although these studies investigated

high-risk patients for cardiovascular events, they did not investigate target groups for effective homocysteine lowering with folic acid and other B vitamins.
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In Reply:

1. Letter by Lorenzl, Linnebank, and Stanger on B vitamins and cerebral ischemia:

In our article on the secondary prevention of stroke, we concentrated on large, randomized studies – for a good reason – and presented the evaluation of the primary end points defined in the study protocol for each of the studies. Within the constraints of an overview, it is not possible to include all post hoc analyses and letters to the editor about this topic. Furthermore, we are of the opinion that for therapeutic decisions mainly predefined end points of clinical studies should be considered – as is the case with licensing studies for new drugs.

2. Letter by Martin Gernken:

All meta-analyses published recently have shown that there is no relation between the dose of aspirin at doses ≥ 30 mg/day and the reduction in vascular end points. The aspirin dose in the ESPRIT study was therefore sufficiently high. An NNT of 80/year is clinically relevant, we think, when bearing in mind that for antihypertensive drugs, the NNT is 110 and for statins it is 230 to 250.

3. Letter by Günther Egidi:

3.1. At the time when the PROGRESS study was planned, the definition for hypertension still meant blood pressure measurements $>160/90$ mm Hg. What is relevant is the principle and not the threshold value by which hypertension is defined.

3.2. The MOSES study was not statistically powered to evaluate secondary end points such as death. It is irrelevant whether nitrendipine was underdosed in the author's opinion, since the blood pressure reduction was identical in both treatment groups. Of all hypertension studies that have been conducted so far, MOSES has the largest proportion of patients whose hypertension was being controlled in the context of the study.

3.3. A difference of normotensive patients in the LIFE study of 46% versus 49% is neither relevant nor does it reach significance.

3.4. The SPARCL study was the first prospective, randomized study that showed the benefit of a statin in secondary prevention of stroke. We kept the recommendation of atorvastatin in the subjunctive because of the drugs costs and licence, and we also explicitly pointed out that lowering cholesterol with a statin is more important than using a particular statin to do so.

3.5. As mentioned above, the aspirin doses in ESPS2 and ESPRIT are definitely effective.

3.6. The authors refute the idea of conflicting interests as mentioned by the first author. The recommendations from the UK National Institute for Health and Clinical Excellence (NICE), which is completely above any suspicion of representing the interests of the pharmaceutical industry, go even further than the authors' in this overview. NICE recommends the combination of aspirin and dipyridole as first line secondary prevention in patients with ischemic stroke, independent of the risk of recurrence.

4. Professor Meyer from Groß-Rodensleben, in a letter directly to us, has pointed out an error. In table 1 in the ESPS2 study, the study end point was stroke. The corrected results should read for dipyridole and ASA, 9.5%, for dipyridole 12.8%, for ASA 12.5%, and for placebo 15.2%. Table 2 also has a mistake. The remarks regarding the comparison of ASA plus dipyridole versus aspirin should say "the combination is significantly more effective than ASA."
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