**Secondary Stroke Prevention: Recent Advances**

Hans-Christoph Diener, Martin Grond, Michael Böhm, Hans-Henning Eckstein, Michael Forsting

**SUMMARY**

**Introduction:** Patients who have suffered a TIA or ischemic stroke have a 5 to 15% annual risk of recurrent stroke. This underlines the need for secondary prevention based on the pathophysiology of the initial event. **Methods:** Selective review of recently published randomized trials in secondary stroke prevention. **Results:** Second generation antihypertensive drugs are effective for secondary prevention of stroke. Atorvastatin at a dose of 80 mg is more effective than placebo. The combination of aspirin and dipyridamole is more effective than aspirin monotherapy whereas the combination of aspirin and clopidogrel is neither superior to aspirin nor to clopidogrel. Oral anticoagulation is not superior to aspirin in patients with non cardiac sources of embolism. The combination of aspirin and clopidogrel is also inferior to oral anticoagulation with warfarin in patients with atrial fibrillation. The treatment of high homocysteine level with vitamin B and folic acid does not prevent stroke. The optimal treatment of symptomatic high grade carotid artery stenosis is still a matter of debate. The complication rate is lower with endarterectomy than with stenting. In addition there are no data yet to suggest that stenting is able to prevent ipsilateral stroke in the long run. 

Key words: secondary stroke prevention, vascular risk factor, antiplatelet drug, statin, atrial fibrillation, stenosis of the internal carotid artery

Patients who have had a transient ischemic attack (TIA) or a first ischemic infarction are at high risk of first or recurrent stroke. Secondary prevention is therefore of eminent importance. In recent years, many randomized studies have been published whose results have implications for secondary drug prevention in stroke. This review summarizes the studies’ findings and reports the practical consequences of the studies’ results. The authors did a selective literature search on Medline and reviewed bibliographies from German, European, and American guidelines. More detailed information can be found in the German and American guidelines (1, 2). Table 1 lists the studies in detail, and table 2 shows the most important recommended treatments with absolute risk reductions and numbers needed to treat (NNT).

**Arterial hypertension**

Arterial hypertension is the most important risk factor for stroke and recurrent stroke after TIA or a first stroke. Fewer studies exist on the role of antihypertensive therapy in secondary prevention than on primary prevention of stroke. The PROGRESS study showed that in 6105 patients, whose acute event dated back a considerable time in some cases, over 5 years of combined treatment with the angiotensin converting enzyme (ACE) inhibitor perindopril and the diuretic indapamide resulted in an absolute risk reduction of 4% for recurrent stroke compared with placebo (3). Perindopril alone was no more effective than placebo. The risk reduction found for the combination was seen in patients with raised or normal blood pressure. Sartans, a modern class of antihypertensive drugs, have biological effects in the primary prevention of stroke that apparently exceed those of mere blood pressure lowering (4). In the MOSES study, 1405 patients with arterial hypertension and transient or permanent cerebral ischemia were treated either with the angiotensin receptor blocker eprosartan or the calcium antagonist nitrendipin over a mean period of 2.5 years. In
both groups, a significant and absolutely identical reduction of blood pressure measurements was observed. With regard to the primary end points – overall mortality and cardiovascular and cerebrovascular events including recurrences – a 3.5% absolute risk reduction was found for eprosartan, which reached significance (5). With regard to cerebrovascular events, the following findings were reported: stroke: 31 (eprosartan) versus 39 (nitrendipin); TIA: 66 versus 92; hemorrhages: 5 versus 3. The benefits of telmisartan compared with placebo in addition to usual antihypertensive medication in secondary prevention of stroke is currently being investigated in the PrOfESS study, which has recruited more than 20 000 patients and whose follow-up concludes at the end of 2007. This study also investigates whether a sartan has neuroprotective properties (reduction of the severity of recurrent stroke) and whether it is capable of preventing or slowing down the development of vascular dementia (6).

In secondary prevention overall, lowering raised blood pressure measurements is more important than the use of a specific antihypertensive drug. In secondary prevention of stroke, the combination of an ACE inhibitor with a diuretic has a protective effect in patients with normal blood pressure, whereas ACE inhibitors alone were found to be no more effective than placebo (3). ACE inhibitors were significantly superior to calcium antagonists in the prevention of vascular events in patients with identical blood pressure measurements. The study results will have to be replicated before the general use of these groups of substances in secondary stroke prevention can be recommended.

Hyperlipidemia

Raised cholesterol and raised triglycerides are risk factors for ischemic events, especially for cerebral large vessel disease with hemodynamically relevant stenoses of arteries supplying the brain and the occurrence of atherosclerotic plaques (7). The main insights into the preventive effect of statins come from studies that were either conducted in the context of primary prevention or mostly in patients with coronary heart disease.

The statin studies that exist usually include patients many years after the qualifying event, i.e., at a time when the recurrence rate is low. This also explains why administering simvastatin has prevented cardiovascular events in stroke patients but not recurrent strokes (8).

The SPARCL study randomized 4731 patients with TIA or stroke, whose cholesterol measurements were between 100 mg/dl and 190 mg/dl and who had no clinical signs of coronary heart disease, to atorvastatin 80 mg or placebo (9). After an average observational period of 5 years, an absolute risk reduction of 2.2% for recurrent stroke was observed for atorvastatin. The number of cerebral hemorrhages, however, increased with atorvastatin treatment (33 placebo versus 55 atorvastatin).

According to the current data situation – one randomized and placebo controlled study – patients with TIA or ischemic stroke without coronary heart disease, whose LDL measurements are 100 to 190 mg/dl, will have to take 80 mg atorvastatin per day in order to reduce the risk of recurrence or cardiovascular morbidity. In view of the price of atorvastatin and the required supplementary payment, this would encounter considerable difficulties. Whether lowering LDL cholesterol – comparable to the recommendations from studies of myocardial infarction/coronary heart disease – is more important than the selection and dosage of a specific statin remains to be seen (1, 10).

Antiplatelet drugs

In patients without cardiac source of embolism, low dose acetylsalicylic acid (aspirin) has been used for secondary prevention since the 1960s. This prophylaxis has resulted in a relative risk reduction of 13% and an absolute risk reduction of 1% per year. The ESPS 2 study published in 1996 showed that the combination of low dosage aspirin with slow release dipyridamole was twice as effective in secondary stroke prevention as aspirin alone (11). The industry independent ESPRIT study included 2739 patients with TIA or mild stroke who were treated either with aspirin at dosage of 30 to 325 mg/day alone or who additionally received dipyridamole 200 mg twice daily (12). 83% of patients took dipyridamole in extended release form. After a mean observation period of 3.5 years, the rate of primary end points – vascular death, stroke, myocardial infarction, or severe hemorrhage – was 16% in the group taking aspirin only and 13% in the group receiving aspirin plus dipyridamole. In spite of methodological deficiencies (open study design, high
<table>
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<tr>
<th><strong>TABLE 1</strong></th>
<th>List of studies included in this review</th>
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<td><strong>Inclusion criteria</strong></td>
<td><strong>No of patients and intervention</strong></td>
</tr>
<tr>
<td><strong>SPACE</strong></td>
<td>Symptomatic (≤ 180 d) carotid stenosis &gt; 70% on Doppler ultrasonography &lt; 50% according to NASCET</td>
</tr>
<tr>
<td><strong>EVA–3S</strong></td>
<td>Symptomatic (≤ 120 d) carotid stenosis &gt; 70% or &gt; 60% as per NASCET (angio or Doppler+ MRA)</td>
</tr>
<tr>
<td><strong>PROGRESS</strong></td>
<td>Stroke/TIA ≤ 5 years</td>
</tr>
<tr>
<td><strong>HPS (cerebrovascular subgroup)</strong></td>
<td>Stroke/TIA or carotid intervention &gt; 6 months, cholesterol &gt; 135 mg/dl and ≤ 180 mg/dl</td>
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<tr>
<td><strong>SPARCL</strong></td>
<td>Stroke/TIA ≤ 6 months without coronary heart disease, LDL cholesterol &gt; 130 mg/dl and ≤ 190 mg/dl</td>
</tr>
<tr>
<td><strong>MOSES</strong></td>
<td>Stroke/TIA or hypertension requiring treatment</td>
</tr>
<tr>
<td><strong>ESPS2</strong></td>
<td>Stroke/TIA ≤ 3 months</td>
</tr>
<tr>
<td><strong>ESPRIT (Antiplatelet drugs)</strong></td>
<td>TIA/atherothrombotic stroke ≤ 6 months</td>
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<tr>
<td><strong>ESPRIT (Anti-coagulation)</strong></td>
<td>TIA/atherothrombotic stroke &lt; 6 months</td>
</tr>
<tr>
<td><strong>CAPRIE</strong></td>
<td>Myocardial infarction ≤ 35 days/ symptomatic PAD/stroke ≤ 6 months</td>
</tr>
<tr>
<td><strong>MATCH</strong></td>
<td>Stroke/TIA ≤ 3 months + ≥ 1 vascular risk factor</td>
</tr>
<tr>
<td><strong>CHARISMA</strong></td>
<td>Atherothrombotic risk factors/CHD/ TIA or stroke ≤ 5 years/symptomatic PAD</td>
</tr>
<tr>
<td><strong>ACTIVE-W</strong></td>
<td>Atrial fibrillation + ≥ 1 stroke risk factor</td>
</tr>
<tr>
<td><strong>VISP</strong></td>
<td>Stroke ≤ 120 days</td>
</tr>
<tr>
<td><strong>NORVIT</strong></td>
<td>Myocardial infarction ≤ 7 days</td>
</tr>
<tr>
<td><strong>HOPE</strong></td>
<td>CHD/PAD/stroke &gt; 1 month Diabetes + ≥ 1 vascular risk factor</td>
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NASCET, North American Symptomatic Carotid Endarterectomy Trial; ASA, acetylsalicyclic acid; HR, hazard ratio; NS, did not reach significance; *1 for non-inferiority; summary of inclusion criteria, end points, and results of the studies discussed in the article.

dropout rate in the dipyridamole arm because of headaches), this study replicates the results of the original ESPS 2 study and emphasizes that the combination of aspirin and dipyridamole is significantly more effective than monotherapy with acetylsalicylic acid. This form of secondary prevention should in future be regarded as standard treatment for patients after TIA and ischemic insult. Interestingly, combining aspirin and dipyridamole did not result in an increase in serious hemorrhagic complications or cardiac events.

The ESPRIT study had a third arm whose results were published at a later date (13). In this arm, 536 patients received oral anticoagulation, with a target INR of 2.0 to 3.0. The results were compared with those of 532 patients who had received monotherapy with aspirin at a dosage of 30 to 325 mg/day over a mean observation period of 4.6 years. The primary combination end points of vascular death, stroke, myocardial infarction, or severe hemorrhage were reached by 18% in the group taking aspirin and by 19% in the anticoagulation arm. The difference did not reach significance. In a post hoc analysis, 523 patients having anticoagulation treatment were compared with 509 patients taking aspirin plus dipyridamole; 20.3% and 16.1%, respectively, of patients reached the primary end point.

In conclusion, anticoagulant treatment with a target INR of 2.0 to 3.0 is not more effective than monotherapy with aspirin and inferior to combination treatment with aspirin and dipyridamole in the secondary prophylaxis after atherothrombotic stroke or TIA.

The CAPRIE study showed that in patients with myocardial infarction, stroke, or peripheral arterial occlusive disease (PAOD) clopidogrel 75 mg compared to 325 mg acetylsalicylic acid leads to an absolute risk reduction of 0.5% for further vascular events per year (14). A subgroup analysis showed no advantage for clopidogrel in patients with stroke as the qualifying event. In patients with ischemic insult and PAOD, clopidogrel is still the drug of choice according to the CAPRIE study’s results. Clopidogrel is given to patients that cannot tolerate aspirin or in whom using aspirin is contraindicated. A comparison between monotherapy with clopidogrel and combined aspirin plus dipyridamole is currently being investigated in the PROFESS study (6).

Another option for combination treatment with 2 antiplatelet drugs is that of aspirin plus clopidogrel. This therapeutic principle has proved valuable in acute myocardial infarction and instable angina pectoris (15) and in stenting of the coronary arteries. All studies have shown a reduction in vascular events, albeit at a higher risk of hemorrhagic complications.
This does not apply in the context of neurology. The MATCH study (16), which compared combination treatment with aspirin and clopidogrel with clopidogrel monotherapy in stroke patients, as well as the CHARISMA study (17), which compared combination treatment with aspirin and clopidogrel and aspirin monotherapy in patients with vascular disease and risk patients, did not show that combination treatment was superior to monotherapy. Combination treatment with aspirin and clopidogrel resulted without exception in a higher number of hemorrhagic complications.

Currently therefore, in the absence of evidence from randomized studies, combination treatment with clopidogrel (75 mg) and aspirin (100 mg) is recommended only in patients with recurrent TIAs, quickly recurring cerebral ischemias, or symptomatic intracranial stenosis, for a time period of no longer than 3 months, and in patients after stenting in intracranial and extracranial stenosis of the arteries supplying the brain for a period of 3 to 6 months (in coated intracranial stents possibly for longer than that).

**Atrial fibrillation and absolute arrhythmia**

Atrial fibrillation (AF) and absolute arrhythmia are important risk factors for stroke. Depending on accompanying illnesses and other vascular risk factors, the risk is 5 to 10% per year. A secondary prevention study conducted many years ago showed that oral anticoagulation compared with placebo lowers the risk of stroke by 8% (ARR); the most favorable balance between risk reduction of cerebral ischemia and hemorrhagic complications was achieved with INR values of 2.0–3.0 (18). Currently, several thrombin antagonists are studied with regard to their indication in primary and secondary prevention of stroke with atrial fibrillation. This group of substances has the advantage of fewer interactions with foods and other drugs than the oral anticoagulants that are currently available and that regular coagulation measurements are not required.

The ACTIVE study investigated the question whether the combination of aspirin and clopidogrel is more effective in patients with atrial fibrillation and has fewer hemorrhagic complications than oral anticoagulation with warfarin (19). The study included 6706 patients, of whom some had already had cerebral ischemia. This is a combined primary and secondary prevention study in which the proportion of patients without TIA or stroke was higher. The study was stopped prematurely because the risk of reaching the primary end points vascular death or stroke, myocardial infarction, and systemic embolism was 3.9% in the anticoagulation group and in the group receiving aspirin and clopidogrel, 5.6%. Surprisingly, the combination of 2 platelet inhibitors did not yield a lower rate of bleeds than oral anticoagulation.

For this reason, all patients without explicit contraindications (non-manageable arterial hypertension, advanced cerebral microangiopathy, dementia, or high risk of falls) should receive oral anticoagulation.

**Other risk factors**

Raised homocystein is a reproducible risk factor for cerebral ischemia and myocardial infarction. 4 large randomized studies have shown unanimously that combination therapy with vitamin B6, B12, and folic acid is able to lower raised concentrations of homocystein but not effective in preventing cerebrovascular or cardiovascular events. This form of secondary prevention is thus obsolete. For a long time, it was postulated that hormone replacement therapy in postmenopausal women has protective effects with regard to myocardial infarction and stroke. This has been disproved for primary as well as secondary prevention. Hormone replacement after menopause increases the risk of vascular events (20).

**Symptomatic carotid stenosis**

Patients with a stenosis of the internal carotid artery of more than 70%, with accompanying TIA (including amaurosis fugax), or ischemic stroke have a high risk of recurrence. Two large studies from North America and Europe showed more than 10 years ago that carotid endarterectomy (CEA) results in an absolute risk reduction for ischemic stroke of 2.5%. Post hoc analyses have shown that the benefits of the operation are greater the higher the extent of the stenosis and the faster it is performed after the qualifying event. For a few years, stent implantation with or without balloon angioplasty has been available as an alternative treatment option. In Germany, this procedure is increasingly being performed,
although until recently no scientific evidence was available to show that this procedure entails the same risks and long term results as CEA. Studies undertaken to date – some of them industry sponsored – have shown contradictory results with very divergent complication rates.

The SPACE study conducted in Germany, Austria, and Switzerland included patients with symptomatic carotid stenosis of over 70%, who either received stents or had carotid endarterectomies (21). Altogether 1200 patients were randomized whose qualifying event had occurred within the last 6 months. The primary end points ipsilateral stroke or death within 30 days occurred in 6.84% of stented patients and in 6.34% of operated patients. The low trend in favor of surgery was also seen in secondary end points. Using a protective system had no influence on the complication rate associated with stenting.

The French EVA-3S study included 527 patients with carotid stenoses in excess of > 60% (22). The study was halted prematurely because in the group of stented patients, stroke of any location or death occurred in 9.6% of cases within 30 days, compared with 3.9% in the surgery group. It had been critically commented that comparatively many inexperienced neurologists and neuroradiologists participated in EVA-3S. A clear association between the number of stenting procedures and the complication rate was not identified, however.

Stent supported angioplasty is currently not the procedure of choice for the treatment of symptomatic carotid stenosis and should be performed only by highly experienced interventionalists. Stenting should, however, be considered in patients with recurrent stenoses after surgery, high grade stenosis after radiotherapy, in highly located stenoses, and those that are difficult to reach with a surgical procedure, and in patients at high risk of general anesthesia. Patients with symptomatic carotid stenosis should receive information about both methods. Ideally, an interdisciplinary decision should be reached after thorough analysis of all accompanying factors (location of the stenosis, age of patient, anesthetic risk, experience of operating specialist) as to whether a stenosis of the internal carotid artery is better treated surgically or in an endovascular fashion. No data exist for asymptomatic carotid stenoses that might be used to compare both procedures.

Conflict of Interest Statement
Professor M Diener has received honorariums for participation in clinical studies, as the principal investigator, member of an advisory board, or for presentations, from: Abbott, AstraZeneca, Bayer Vital, Boehringer Ingelheim, D-Pharm, Fresenius, GlaxoSmith-Kline, Janssen Cilag, MSD, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Sankyo, Servier, Solvay, Weyth, Yamaguchi. Research projects were financially supported by AstaZeneca, GSK, Boehringer Ingelheim, Novartis, Janssen-Cilag, Sanofi-Aventis. The university hospital for neurology in Essen is in receipt of research funding from the EU, Deutsche Forschungsgemeinschaft (German Research Foundation), Federal Ministry of Education and Research, Bertelsmann Foundation, and Heinz-Nixdorf Foundation. H-C Diener does not hold stocks or shares in pharmaceutical companies.

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Professor H-H Eckstein is a steering committee member of the SPACE study and director of the standards committee for surgical therapy within the SPACE study. H-H Eckstein has received honoraria as an advisory board member or for presentations from Novartis and Medtronic. The department of vascular surgery at the Klinikum Rechts der Isar of the Technical University of Munich is in receipt of financial support for clinical research projects from Sanofi-Aventis and of research grants from the German Federal Ministry of Education and Research and the Deutsche Forschungsgemeinschaft (German Research Foundation). H-H Eckstein does not hold stocks or shares in pharmaceutical companies or manufacturers of medical equipment.

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