Update of secondary stroke prevention

Hans-Christoph Diener and Christian Weimar

Department of Neurology and Stroke Center, University Hospital Essen, Hufelandstrasse 55, 45147 Essen, Germany

Correspondence and offprint requests to: Hans-Christoph Diener; E-mail: hans.diener@uni-due.de

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Introduction

Secondary prevention aims at preventing a stroke after a transient ischaemic attack (TIA) or a recurrent stroke after a first stroke. About 80–85% of patients survive a first ischaemic stroke [1,2]. Of those, between 8 and 15% suffer a recurrent stroke in the first year. The risk of stroke recurrence is highest in the first few weeks and declines over time [3–5]. The risk of recurrence depends on concomitant vascular diseases (coronary heart disease = CHD, peripheral arterial disease = PAD) and vascular risk factors and can be estimated by risk models [6–8]. Stroke risk after a TIA is highest in the first 3 days [9]. Therefore, immediate evaluation of patients with a stroke or TIA, identification of the pathophysiology and initiation of secondary prevention are of major importance [10]. In the following sections, we will deal with the treatment of risk factors, antithrombotic therapy and surgery or stenting of significant stenosis of extracranial arteries.

Hypertension

There are very few studies investigating the efficacy of different classes of antihypertensive drugs in secondary stroke prevention. One has to remember that two concepts exist in this field. Placebo-controlled trials may try to achieve a maximum of blood pressure lowering in patients with high blood pressure. Vascular protective trials like HOPE [11] include patients with vascular risk factors even with normal blood pressure under the assumption that end organs such as the brain will be protected. A meta-analysis comprised seven studies in 15 527 patients with TIA, ischaemic or haemorrhagic stroke followed for 2–5 years. Treatment with antihypertensives reduced the risk of stroke by 24%, risk of non-fatal stroke by 21%, risk of myocardial infarction (MI) by 21% and the risk of all vascular events by 21% [12]. For the endpoint stroke, the combination of an ACE inhibitor with a diuretic was more effective (45% risk reduction) than a diuretic as monotherapy (32%), monotherapy with an ACE inhibitor (7% ns) or a beta-blocker (7%).

ACE inhibitors and ARBs are supposed to have pleiotropic and protective vascular effects beyond lowering high blood pressure. Therefore, the HOPE study compared ramipril with placebo. In the subgroup of patients with TIA or stroke as the qualifying event, ramipril resulted in a relative reduction of the combined endpoint of stroke, MI or vascular death by 24% and an absolute risk reduction of 6.3% in 5 years [13].

PROGRESS was the first large-scale trial specifically performed in patients after stroke. A total of 6105 patients were treated with perindopril as monotherapy or in combination with indapamide or placebo. Across the 4 year-observation time, the blood pressure was lowered on average by 9/4 mmHg. The absolute risk reduction for recurrent stroke was 4%, and the relative risk reduction (RRR) was 28%. Monotherapy with the ACE inhibitor was not only superior to placebo but also did not achieve the same level of blood pressure lowering than the combination therapy. The RRR for combination therapy was 43% [14]. ACCESS was a small phase II safety study in stroke patients with high blood pressure (>200/110 mmHg) in the early phase after an acute stroke. The patients were randomized to receive either candesartan or placebo in the first 7 days after stroke and continued with candesartan [15]. In the 12 month observation period, the rate of vascular events was significantly lower in the candesartan group (9.8% versus 18.7%, RRR = 52%). One has to consider, however, that ACCESS was planed as a safety study and was not powered as an endpoint study for the prevention of vascular events.

MOSES included 1352 patients with hypertension who had suffered a stroke in the last 24 months. The patients were treated either with eprosartan (600 mg) or with nitrendipin (10 mg) on top of additional antihypertensive therapy when appropriate. For an identical drop in blood pressure, eprosartan was superior to nitrendipin to prevent recurrent vascular events (21% RRR). The optimal systolic blood pressure in the MOSES trial was 120–140 mmHg. PROGRESS randomized 20 332 patients with a recent ischaemic stroke to receive telmisartan at 80 mg/day or placebo in addition to other therapies, for a median duration of 2.4 years. The mean blood pressure over the trial period was lower in the telmisartan group by 3.8/2.0 mmHg. Recurrent strokes occurred in 8.7% in the telmisartan group.
High cholesterol

The association of cholesterol levels with the risk of recurrent stroke is lower than the association with the risk of MI. Statins will, however, lower the risk of stroke in patients with CHD [17]. The RRR calculated from a meta-analysis is 21% [18]. NCEP ATP III guidelines recommend treating stroke patients with CHD with a statin. The LDL cholesterol level should be <100 mg/dl for patients with low or moderate risk and <70 mg/dl in high-risk patients [19].

Patients with stroke without CHD were investigated in a subgroup of the Heart Protection Study (HPS) and the SPARCL trial. Within the HPS patient population of 20 536 high-risk patients, 3280 patients had TIA or stroke and 1820 of them without concomitant CHD. The RRR achieved by simvastatin given for 5 years for vascular events was 20% and the absolute risk reduction 5.1% [20]. In the overall population, the RRR for stroke was 25% whereas there was no significant reduction in the stroke rate in the subgroup of patients with TIA or stroke as the qualifying event [21].

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was performed in 4731 patients with TIA or stroke without CHD and LDL cholesterol levels between 100 and 190 mg/dl. The patients received either 80 mg atorvastatin or placebo. After an average of 4.9 years, the primary endpoint (stroke) was reduced by 16% relative and 2.2% absolute [22]. The discrepancy with the HPS trial might be explained by the fact that HPS recruited patients on average 4.3 years after the initial vascular event whereas this time interval was only 6 months in SPARCL. The RRR for the combined endpoint of stroke, MI and vascular death was 20 and the ARR 3.5 years. The rate of ischaemic stroke was reduced (218 versus 274) whereas haemorrhagic strokes were more frequent with atorvastatin (55 versus 33).

Therapy with a statin should be initiated early after an ischaemic stroke or TIA. The sudden discontinuation of a statin in patients with a stroke or acute coronary syndrome might be associated with higher morbidity and mortality [23,24]. Therefore, patients on a statin should continue treatment following an acute ischaemic event.

Diabetes mellitus

Randomized controlled studies were unable to show an effect of glitazones on vascular events in stroke patients with diabetes mellitus [25]. Aggressive lowering of blood glucose does not reduce the risk of stroke [26] and might even increase mortality [27]. Therefore, treatment of diabetes mellitus should not be restricted to drug treatment but should also apply to diet, weight loss and regular exercise.

Supplementation of vitamins

The VISP study was unable to show a benefit of the treatment of high homocysteine in stroke patients with B vitamins and folic acid [28]. The HOPE-2 study also failed to demonstrate benefit [29]; the study included 5522 patients aged >55 years and a vascular event or diabetes mellitus and treated them for 5 years with either placebo or 2.5 mg folic acid, 50 mg vitamin B6 and 1 mg vitamin B12. This resulted in a significant reduction in homocysteine levels but not in vascular events. Supplementation of vitamins E or C is also not able to prevent strokes or recurrent strokes [30,31].

Hormone replacement therapy after menopause

A randomized, placebo controlled study in women who suffered a stroke receiving hormone replacement therapy after menopause found an increase in stroke mortality and a poorer prognosis in non-fatal strokes [32]. Therefore, in general, hormone replacement should be avoided following a stroke.

Antiplatelet therapy

Antiplatelet drugs are effective in secondary stroke prevention after TIA or ischaemic stroke. This has been shown in many placebo-controlled trials and in several meta-analyses [33–35]. The RRR for non-fatal stroke achieved by antiplatelet therapy in patients with TIA or stroke is 23% (reduced from 10.8% to 8.3% in 3 years) [34]. The combined endpoint of stroke, MI and vascular death is reduced to 17% (from 21.4% to 17% in 29 months).

A meta-analysis of the 11 randomized and placebo-controlled trials investigating acetylsalicylic acid (ASA) monotherapy in secondary stroke prevention found a RRR of 13% [95% confidence intervals (CI) 6–19%] for the combined endpoint of stroke, MI and vascular death [36]. There is no relationship between the dose of ASA and its efficacy in secondary stroke prevention [34,36,37]. Therefore, the recommended dose of ASA is 75–150 mg/day. Gastrointestinal adverse events (AEs) and bleeding complications are, however, dose dependent, and bleeding rates increase significantly beyond a daily dose of ASA of 150 mg [38,39].

Clopidogrel monotherapy (75 mg/day) was compared to ASA (325 mg/day) in almost 20 000 patients with stroke, MI or PAD. The combined endpoint of stroke, MI and vascular death showed a RRR of 8.7% in favour of clopidogrel. The ARR was 0.51% [40]. The highest benefit of clopidogrel was seen in patients with PAD. The risk of GI bleedings (1.99% versus 2.66%) and GI side effects (15% versus 17.6%) was smaller with clopidogrel than with ASA.

The MATCH study compared the combination of clopidogrel 75 mg and ASA 75 mg with clopidogrel monotherapy in high-risk patients with TIA or ischaemic stroke [41] and failed to show superiority of combination antiplatelet therapy for the combined endpoint of stroke, MI, vascular death and hospitalization due to a vascular event. The
combination resulted in a significant increase in bleeding complications, and therefore is not recommended.

The CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) was a combined primary and secondary prevention study in 15 603 patients that compared the combination of clopidogrel and ASA with ASA monotherapy [42]. Similar to MATCH, the study failed to show a benefit for combination therapy and displayed a higher bleeding rate with the combination. Symptomatic patients, however, showed a trend towards a benefit for combination antplatelet therapy [43].

The combination of low-dose ASA and extended-release dipyridamole (ER-DP) was investigated in the second European stroke prevention study (ESPS2) with 6602 patients with TIA or stroke [44]. The patients were randomized to ASA (25 mg bid), ER-DP (200 mg bid), the combination of ASA and ER-DP or placebo. For the primary endpoint stroke, the combination was superior to ASA monotherapy (RRR 23%, APR 3%) and placebo (RRR 37%, ARR 5.8%).

ASA monotherapy lowered the risk of stroke by 18% (ARR 2.9%) and dipyridamole monotherapy by 16% (ARR 2.6%) compared to placebo. Major bleeding complications were seen more frequently with ASA and the ASA + ER-DP combination, whereas DP monotherapy had a similar bleeding rate as placebo. Cardiac events occurred in similar frequency in the groups treated with dipyridamole compared to ASA [45]. The industry-independent ESPRIT study [46] randomized 2739 patients with presumed atherothrombotic TIA or minor stroke to ASA (30–325 mg) or the combination of ASA with DP and followed them for a mean period of 3.5 years. The primary endpoint was the combination of vascular death, stroke, MI and major bleeding complications. The event rate for the primary endpoint was 16% with ASA monotherapy and 13% with ASA + DP resulting in a RRR of 20% (ARR 1%). In the combination arm, 34% of patients terminated the trial prematurely mostly because of AEs like headache (13% in the ASA arm of the study). A meta-analysis of all stroke prevention trials testing ASA monotherapy versus ASA + DP showed a RRR in favour of the combination for the combined vascular endpoint by 18% (95% CI 9–26%) [46].

A head-to head comparison of clopidogrel with ASA + ER-DP was performed in the PRoFESS study [47]. The study randomized 20 332 patients with ischaemic stroke and followed them for a mean period of 2.4 years. There was no difference in efficacy across all endpoints and various subgroups of patients. ASA plus ER-DP resulted in more intracranial bleedings and a higher drop out rate due to headache compared with clopidogrel (5.9% versus 0.9%).

Table 1 gives an overview of absolute and relative risk reductions for different approaches in secondary stroke prevention. The calculation of the Essen risk score is shown in Table 2 [7,48,49].

Glycoprotein-IIb/IIIa-receptor antagonists are effective in the acute coronary syndrome [50]. Oral GP-IIb-IIIa-antagonists are not superior to ASA and carry a higher bleeding risk as shown in the BRAVO trial [38].

### Table 1. Strategies for prevention of recurrent stroke after an initial TIA or ischaemic stroke

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Relative RR</th>
<th>Absolute RR/year</th>
<th>NNT/year</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive therapy</td>
<td>24%</td>
<td>0.46%</td>
<td>217</td>
<td>Proven for perindopril + indapamide and eprosartan</td>
</tr>
<tr>
<td>Statins</td>
<td>16%</td>
<td>0.4%</td>
<td>250</td>
<td>Proven for atorvastatin and simvastatin</td>
</tr>
<tr>
<td>ASA 50–150 mg after TIA or ischaemic stroke</td>
<td>18–22%</td>
<td>1.3%</td>
<td>77</td>
<td>ASA doses ≥ 150 mg = higher bleeding risks</td>
</tr>
<tr>
<td>ASA 50 mg + dipyridamole 400 mg versus ASA</td>
<td>23%</td>
<td>1.0–1.5%</td>
<td>67–100</td>
<td>Combination also superior to placebo</td>
</tr>
<tr>
<td>Clopidogrel versus ASA</td>
<td>8%</td>
<td>0.5%</td>
<td>200</td>
<td>Based on a subgroup analysis from CAPRIE</td>
</tr>
<tr>
<td>Surgery of a high-degree carotid stenosis*</td>
<td>65%</td>
<td>3.1%</td>
<td>32</td>
<td>Efficacy declines with time interval from event</td>
</tr>
<tr>
<td>ASA in high-degree intracranial stenosis</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>In comparison to warfarin there was no significant benefit</td>
</tr>
<tr>
<td>Oral anticoagulation in cardiogenic source of embolism (AF) INR 3.0</td>
<td>68%</td>
<td>8%</td>
<td>12</td>
<td>Only one placebo-controlled study available (EAFT)</td>
</tr>
<tr>
<td>ASA in AF</td>
<td>19%</td>
<td>2.5%</td>
<td>40</td>
<td>In patients with contraindications for warfarin</td>
</tr>
</tbody>
</table>

NNT = number needed to treat/year, RR = risk reduction, AF = atrial fibrillation.

*Outcome stroke and death.

### Table 2. Essen risk score for the calculation of the risk of a recurrent stroke after an initial ischaemic stroke of atherothrombotic origin

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 years</td>
<td>0</td>
</tr>
<tr>
<td>Age 65–75 years</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Other cardiovascular events</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
</tr>
<tr>
<td>Additional TIA or ischaemic stroke</td>
<td>1</td>
</tr>
</tbody>
</table>

A score of ≥3 points indicates a recurrence risk of ≥4%/year.
more effective than ASA for the prevention of vascular events (OR 0.67; 95% CI 0.50–0.91) or recurrent stroke (OR 0.49; 95% CI 0.33–0.72) [52]. The risk of major bleeding complications is significantly increased but not the risk of intracranial bleedings. Patients with intermittent AF have a similar stroke risk as patients with permanent AF [53,54]. The optimal INR range for oral anticoagulation is between 2.0 and 3.0 [55]. INR values of >3.0 lead to an increased risk of major bleeding complications, in particular in the elderly [56].

The ACTIVE study [57] compared the combination of ASA and clopidogrel versus oral anticoagulation with warfarin in patients with AF; the study was terminated prematurely due to a significant reduction of stroke and systemic embolism in favour of warfarin. The rate of major bleeding complications was not different between the two regimens.

**Cryptogenic stroke and patent foramen ovale (PFO)**

The prevalence of PFO is up to 25% in the general population. To date, epidemiologic studies have not shown thromboembolic events more frequently in persons with PFO, and therefore no special primary intervention is needed [58]. In patients with stroke of unknown cause (cryptogenic stroke), however, the prevalence of PFO increases to ~40% [59]. Case reports and case-control studies of cryptogenic strokes compared to strokes with known aetiology or non-stroke controls have shown an association of PFO with stroke. Therefore, the question about prevention arises after stroke or emboli to other organs. Prospective cohort studies have shown that treatment with aspirin or warfarin reduces the risk of recurrent stroke in the average patient with PFO to the same risk as in patients without PFO. Aspirin was as effective as anticoagulation and therefore should be given [60]. Among patients with PFO, those with spontaneous or large right-to-left shunts, with a coinciding ASA or multiple ischaemic events prior to the PFO diagnosis, are at higher risk of recurrent stroke than an average PFO patient. Percutaneous device closure (PDC) becomes, therefore, a challenging alternative to medical treatment in such patients, but data from randomized-controlled trials (RCT) comparing the effect of PDC with medical therapy are still missing [61]. At present, general use of PDC cannot be recommended.

**Anticoagulation in cerebral ischaemia of non-cardiac origin**

The Stroke Prevention in Reversible Ischemia trial (ESPRIT) studied oral anticoagulation with an INR between 3.0 and 4.5 versus ASA 30 mg in patients with TIA or minor stroke without cardiac source of embolism [62]. The study was terminated due to a significantly increased bleeding risk with anticoagulation. The risk of bleeding was increased by a factor of 1.43 (95% CI, 0.96–2.13) for an increase of the INR by 0.5. The Warfarin Aspirin Recurrent Stroke Study (WARSS) showed a similar rate of ischaemic events and bleeding complications comparing warfarin (INR 1.4–2.8) and ASA in stroke patients without cardiac source of embolism [63]. This result was replicated in the ESPRIT study [64]. ESPRIT found a lower rate of ischaemic events with anticoagulation counterbalanced by an increased risk of intracranial bleedings.

A Cochrane analysis of five trials with 4076 patients was unable to show that anticoagulants were more or less efficacious in the prevention of vascular events than antiplatelet therapy [medium intensity anticoagulation relative risk (RR) 0.96, 95% CI 0.38–2.42; high intensity anticoagulation RR 1.02, 95% CI 0.49–2.13]. The RR for major bleeding complications for low-intensity anticoagulation was 1.27 (95% CI 0.79 to 2.03) and for medium intensity anticoagulation 1.19 (95% CI 0.59–2.41). High-intensity oral anticoagulants with INR 3.0–4.5 resulted in a higher risk of major bleeding complications (RR 9.0, 95% CI 3.9–21) [65].

The Antiphospholipid Antibodies and Stroke Study (APASS) found no difference in stroke, MI or vascular death in patients with antiphospholipid antibodies (aPL) treated with warfarin (INR 1.4–2.8) compared to 325 mg ASA [66]. There was, in addition, no difference in event rates between patients positive and negative for aPL. The evidence for anticoagulation in patients with protein C, protein S or anti-thrombin deficiency is derived from patients with deep vein thrombosis and not from patients with stroke.

The possible benefit of oral anticoagulation for the long-term treatment of dissections has never been studied in a randomized trial compared to antiplatelet drugs. An observational study from Canada in 116 patients with angiographically proven dissection of the vertebral or carotid arteries found a rate of TIA, stroke or death in the first year to be 15%. The event rate in patients with anticoagulation was 8.3%, and in patients receiving ASA 12.4% the difference was not statistically significant [67]. A Cochrane review of 26 observational studies in 327 patients found no difference between anticoagulation and antiplatelet drugs for the endpoint death and severe disability [68]. A more recent review came to a similar conclusion [69].

**Carotid endarterectomy and stenting with balloon angioplasty**

Two large randomized trials (NASCET and ESC) found a clear benefit of carotid surgery compared to medical treatment in patients with high-degree stenosis of the ICA [70–76]. Taken together, the trials found an absolute risk reduction of 13.5% over 5 years for the combined endpoint of stroke and death in favour of carotid endarterectomy [76]. The risk reduction is even higher in stenosis >90%. In patients with 50–69% ICA stenosis, the 5-year absolute RR for the endpoint ipsilateral stroke is 4.6%. This benefit is mainly seen in men. Patients with <50% ICA stenosis do not benefit from carotid endarterectomy. The short-term complication rates (stroke and death) were 6.2% for stenosis >70% and 8.4% for 50–69% stenosis. ASA should be given prior to, during and after carotid surgery [77].

Several studies randomized patients with significant ICA stenosis to carotid endarterectomy or balloon angioplasty with stenting. Surgeons and interventional neuroradiologists had to pass a quality control. SPACE randomized 1200 symptomatic patients with an >50% stenosis (NASCET
criteria) or >70% (ESC criteria) within 6 months after TIA or minor stroke to carotid endarterectomy or stenting [78]. The primary endpoint, ipsilateral stroke or death within 30 days, was 6.84 in patients undergoing stenting and 6.34% in patients who were operated. A post hoc subgroup analysis identified age <68 years as a factor for a lower complication rate in patients treated with stenting. The complication rate of surgery was not age dependent [79]. The use of the protection system did not influence the complication rate. The EVA3S study was terminated prematurely after 527 patients were randomized due to a significant difference in the 30-day complication rate favouring carotid surgery (9.6% versus 3.9%; OR 2.5; 95% CI 1.25–4.93) [80]. Taken together, the results of the two studies show a lower complication rate for endarterectomy [81]. The reported medium-term outcomes were comparable, and the restenosis rate was higher after carotid stenting.

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References


Predicting outcomes in CKD: the importance of perspectives, populations and practices

Adeera Levin, MD, FRCPC

Division of Nephrology, University of British Columbia, Vancouver, Canada

Correspondence and offprint requests to: Adeera Levin, MD, FRCPC; E-mail: alevin@providencehealth.bc.ca

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The problem of chronic kidney disease (CKD) has been brought into focus over the last 7 years since the publication and dissemination of the KDOQI definition, evaluation and classification of CKD guidelines, and the implementation of eGFR reporting by laboratories in numerous jurisdictions [1]. Together these two 'events' have substantially increased awareness about and focus on CKD in both clinical and academic spheres. Concerns and issues have been raised as to the validity of the stages in all populations, the need for more refinement and the possibility of misclassification and inflated estimates of CKD in populations based on eGFR equations [2,3]. These discussions aside, the ability to report or calculate eGFR has improved the identification of abnormalities of kidney function in persons around the world, and stimulated substantial research into the validation of the equations in different populations, and prediction models for progression to renal replacement therapy (RRT) or death. The increasing appreciation of CKD as a multiplier of risk, and as more common in high-risk populations with CVD and diabetes, has helped to focus attention on these patient groups, and may well permit avoidance of adverse events due to better identification [4,5].

The paper by Conway et al., in this edition of the journal, examines the outcomes of 396 patients with stage 4 CKD referred to nephrology clinics in the UK using electronic databases to determine important outcomes of death, dialysis and rates of progression [6]. The major goal of the study was to identify factors that predict outcomes in CKD patients and whether low-risk patients could be managed in primary care. The authors examined an elderly cohort of patients (71% over the age of 65) in a national health care system, with a substantial primary care infrastructure support. The importance of this study is that it describes outcomes of those patients, who were referred to nephrology care prior to the publication of the KDOQI, and subsequent UK Guidelines for CKD care and before the nationwide eGFR reporting strategy was implemented [7]. In this referred elderly cohort, those over the age of 74 progressed at a rate of ∼0.86 ml/min/1.73 m²/year, substantially slower than those in the other age groups of <65 or between 65 and 74. Interestingly, proteinuria was less with increasing age at referral, and median creatinine was lower in older patients, though eGFR was ∼22 ml/min/1.73 m²,

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