Introduction

Secondary prevention aims at preventing a stroke after a transient ischemic attack (TIA) or a recurrent stroke after a first stroke. About 80–85% of patients survive a first ischemic stroke [1, 2]. Of those between 8% and 15% suffer a recurrent stroke in the first year. 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 artery disease [PAD]) and vascular risk factors and can be estimated by risk models [6, 7]. Stroke risk after a TIA is highest in the first 3 days [8]. Therefore, immediate evaluation of patients with stroke or TIA, identification of the pathophysiology, and initiation of pathophysiology-based treatment is of major importance [9]. In the following sections, we will deal with the treatment of risk factors, antithrombotic therapy, and surgery or stenting of significant stenosis of extra- or intracranial arteries. Each paragraph will be introduced by recommendations, followed by the scientific justification.

Treatment of risk factors

Hypertension

- Early initiation of antihypertensive therapy with telmisartan in addition to standard antihypertensive therapy is not more effective than placebo.
- Most likely all antihypertensive drugs are effective in secondary stroke prevention. Beta-blockers, such as atenolol, show the lowest efficacy. More important than the choice of a class of antihypertensives is to achieve the systolic and diastolic blood pressure targets (<140/90 mmHg in non-diabetics and <130/80 mmHg in diabetics). In many cases this requires combination therapy. Concomitant diseases (kidney failure, congestive heart failure) have to be considered.
- Lifestyle modification will lower blood pressure and should be recommended in addition to drug treatment.

There are very few studies investigating the efficacy of 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 lowering of blood pressure in patients with high blood pressure. Vascular protective studies such as the Heart Outcomes Prevention Evaluation (HOPE) study [10] 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 of 15 527 patients with TIA, or ischemic or hemorrhagic stroke, who were followed for 2–5 years. Treatment with antihypertensives reduced the risk of stroke by 24%, non-fatal stroke by 21%, risk of myocardial infarction (MI) by 21%, and the risk of all vascular events by 21% [11]. 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%), or a beta-blocker (7%).

ACE inhibitors and ARBs were thought 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 (ARR) of 6.3% in 5 years [12].

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was the first large-scale trial specifically performed in patients after stroke. Patients (n = 6105) were treated with perindopril as monotherapy or in combination with indapamide or placebo. Across the 4-year observation time blood pressure was lowered on average by 9/4 mmHg. The ARR for recurrent stroke was 4% and the relative risk reduction (RRR) was 28%. Monotherapy with the ACE inhibitor was not superior to placebo, but also did not achieve the same level of blood pressure lowering as the combination therapy. The RRR for combination therapy was 43% [13].

Acute Candesartan Cilexetil Therapy in Stroke Survivors (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. Patients were randomized to receive either the ARB candesartan or placebo in the first 7 days after stroke and continued with candesartan [14]. In the 12-month observation period the rate of vascular events was significantly lower in the candesartan group (9.8% vs. 18.7%, RRR = 52%).

The Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) study included 1352 patients with hypertension who had suffered a stroke in the previous 24 months. Patients were treated either with eprosartan (600 mg) or with nitrendipine (10 mg) on top of additional antihypertensive therapy when appropriate. For an identical drop in blood pressure, eprosartan was superior to nitrendipine in preventing recurrent vascular events (21% RRR). Optimal systolic blood pressure in the MOSES trial was 120–140 mmHg.

The Prevention Regimen For Effectively avoiding Secondary Stroke (PRoFESS) study randomized 2032 patients with a recent ischemic stroke to receive telmisartan at 80 mg/day or placebo in addition to other therapies, for a median duration of 2.4 years. 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 compared to 9.2% in the placebo group, which was not significant. Therefore initiation of telmisartan early after a stroke, and continuation for a median of 2.4 years, did not significantly lower the rate of recurrent strokes, other major vascular events, or new diabetes [15].

The Secondary Prevention in Small Subcortical Strokes Trial (SPS3) randomized 3020 patients with recent, MRI-confirmed symptomatic lacunar strokes into two blood pressure target groups: 130–140 mmHg or <130 mmHg. Patients were followed for a mean of 3.7 years. The primary outcome was reduction in all stroke, both ischemic and hemorrhagic. After 1 year, the mean blood pressure was 138 mmHg in the higher target group and 127 mmHg in the lower target group. There was no significant difference in the rate of recurrent stroke between the two groups but the rate of intracerebral hemorrhage was significantly reduced in the lower target group [16].

Antihypertensive therapy reduces the risk of stroke. Most likely all antihypertensive drugs are effective in secondary stroke prevention.

In patients with lacunar stroke, there is no additional benefit with a lower systolic blood pressure target of <130 mmHg compared to the conventional target of <140 mmHg.

**High cholesterol**

- Patients with TIA or ischemic stroke and CHD should be treated with a statin irrespective of the initial low-density lipoprotein (LDL) cholesterol level. The target range of LDL is 70–100 mg/dl. Patients with atherosclerotic ischemic stroke or TIA without CHD and LDL cholesterol levels between 100 and 190 mg/dl will benefit from a treatment with 80 mg atorvastatin. Statin therapy reduces the rate of recurrent stroke and vascular events.

- Lowering high LDL is more important than the use of a particular statin. Therefore lowering LDL cholesterol <100 mg/dl or ≥50% of the initial LDL cholesterol level is recommended.

The association of cholesterol levels and the risk of recurrent stroke is not as strong as 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 (National Cholesterol Education Program Adult Treatment Panel III) guidelines recommend treating stroke patients with CHD with a statin. The LDL cholesterol level should be <100 mg/dl 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 trial. Within the HPS patient population of 20 536 high-risk patients, 3280 patients had TIA or stroke, 1820 of them without concomitant CHD. The RRR achieved by simvastatin given for 5 years for vascular events was 20% and the ARR 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]. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) was performed in 4731 patients with TIA or stroke without CHD and LDL cholesterol levels between 100 and 190 mg/dl. 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%. The rate of ischemic stroke was reduced (218 vs. 274) whereas hemorrhagic strokes were more frequent with atorvastatin (55 vs. 33).

Therapy with a statin should be initiated early after an ischemic 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 ischemic event.

Patients with TIA or ischemic stroke and coronary heart disease (CHD) should be treated with a statin irrespective of the initial LDL cholesterol level.

### 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 and might even increase mortality [26, 27]. Therefore, treatment of diabetes mellitus should not be restricted to drug treatment but should also include diet, weight loss, and regular exercise.

### Supplementation of vitamins

- Treatment of increased plasma levels of homocysteine with vitamin B6, vitamin B12, and folic acid is not effective in secondary stroke prevention.

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 who had a vascular event or diabetes mellitus and were treated for 5 years with either placebo or a combination of 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 a reduction of vascular events.

### Hormone replacement therapy after menopause

- Hormone replacement after menopause is not effective in the secondary prevention of stroke and may even increase the risk of fatal strokes.

A randomized, placebo-controlled study in women receiving hormone replacement therapy after menopause who suffered a stroke found an increase in stroke mortality and a poorer prognosis in non-fatal strokes [30]. Therefore, in general, hormone replacement should be avoided following a stroke.

### Antiplatelet therapy

- Patients with TIA or ischemic stroke should receive antiplatelet drugs. The choices are acetylsalicylic acid (ASA 50–150 mg), the combination of ASA (2 × 25 mg) and extended-release dipyridamole (ER-DP 2 × 200 mg) or clopidogrel (75 mg).
- ASA is recommended in patients with a low risk of recurrence (<4%/year). Patients with a higher risk of recurrent stroke should be treated with ASA + ER-DP or clopidogrel. ASA + ER-DP and clopidogrel appear to be equally effective. ASA + ER-DP has more side-effects.
• Doses of ASA >150 mg/day result in an increased risk of bleeding complications.

• The combination of clopidogrel plus ASA is not more effective than either ASA or clopidogrel monotherapy, and carries a higher bleeding risk.

• The efficacy of antiplatelet therapy beyond 4 years after the initial event has not been studied in randomized trials. Theoretically, treatment should continue beyond that period.

• In the case of a recurrent ischemic event the pathophysiology of the ischemic event should be evaluated. When there is an indication for antiplatelet therapy the recurrence risk should be evaluated and the antiplatelet therapy adapted to the new risk. There is no evidence that changing antiplatelet therapy from ASA plus ER-DP to clopidogrel or vice versa provides greater protection.

• Patients with a history of TIA or ischemic stroke and an acute coronary syndrome should receive the combination of clopidogrel and ASA for at least 3 months. The same is true for patients with a coronary stent. This therapy is also typically extrapolated to patients with carotid stents.

• In patients with lacunar stroke, there is no significant benefit of dual antiplatelet therapy with clopidogrel and aspirin over aspirin alone. Moreover, the combination can increase the risk of hemorrhagic side-effects.

• A short-term course of dual antiplatelet therapy may be considered after an acute stroke or TIA.

Antiplatelet drugs are effective in secondary stroke prevention after TIA or ischemic stroke. This has been shown in many placebo-controlled trials and in several meta-analyses [31–33]. 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) [32]. The combined endpoint of stroke, MI, and vascular death is reduced by 17% (from 21.4% to 17% in 29 months).

A meta-analysis of 11 randomized and placebo-controlled trials investigating ASA monotherapy in secondary stroke prevention found a RRR of 13% (95% confidence interval [CI] 6–19) for the combined endpoint of stroke, MI, and vascular death [34]. There is no relationship between the dose of ASA and its efficacy in secondary stroke prevention [32, 34, 35]. Therefore, the recommended dose of ASA is 75–150 mg/day. Gastrointestinal adverse events and bleeding complications are, however, dose-dependent and bleeding rates increase significantly beyond a daily ASA dose of 150 mg [36, 37].

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 favor of clopidogrel. The ARR was 0.51% [38]. The highest benefit of clopidogrel was seen in patients with PAD. The risk of gastrointestinal bleeds (1.99% versus 2.66%) and gastrointestinal side-effects (15% versus 17.6%) were 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 ischemic stroke [39] and failed to show the 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 and compared the combination of clopidogrel and ASA with ASA monotherapy [40]. Similarly to MATCH, the study failed to show a benefit of combination therapy and displayed a higher bleeding rate with the combination. Symptomatic patients, however, showed a trend towards a benefit for combination antiplatelet therapy [41].

The combination of low-dose ASA and ER-DP was investigated in the second European Stroke Prevention Study (ESPS2) with 6602 patients with TIA or stroke [42]. 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 of stroke, the combination was superior to ASA monotherapy (RRR 23%, ARR 3%) and placebo (RRR 37%, ARR 5.8%). ASA monotherapy lowered the risk of stroke by 18% (ARR 2.9%) and DP 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 to placebo. Cardiac events occurred at similar frequency in the groups treated with DP compared to ASA [43]. The industry-independent ESPRIT study [44] 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 adverse events such as 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 of 18% (95% CI 9–26) in favor of the combination for the combined vascular endpoint [44].

A head-to-head comparison of clopidogrel and ASA + ER-DP was performed in the PRoFESS study [45]. The study randomized 20,332 patients with ischemic stroke and followed them for a mean period of 2.4 years. There was no difference in efficacy across all endpoints and no subgroup of patients. ASA + ER-DP resulted in more intracranial bleeds and a higher drop-out rate due to headache compared with clopidogrel (5.9% vs. 0.9%).

Table 22.1 gives an overview of ARR and RRR for different approaches in secondary stroke prevention. The calculation of the Essen risk score is shown in Table 22.2 [8, 46, 47].

Glycoprotein (GP)-IIb/IIIa receptor antagonists are effective in the acute coronary syndrome [48]. Oral GP-IIb/IIIa-antagonists are not superior to ASA and carry a higher bleeding risk as shown in the BRAVO trial [36].

The use of dual antiplatelet therapy in patients with lacunar stroke was investigated in the SPS3 trial, which randomized 3020 patients with recent, MRI-confirmed symptomatic lacunar strokes into two antiplatelet groups: aspirin 325 mg daily and clopidogrel 75 mg daily versus aspirin 325 mg daily and placebo. Patients were followed for a mean of 3.4 years. The primary outcome was reduction in all stroke, both ischemic and hemorrhagic. The risk of recurrent ischemic stroke was not significantly different between the two groups. The risk of major hemorrhage was significantly higher in the dual antiplatelet therapy group, 2.1% per year, compared with 1.1% per year risk in the aspirin-only group. Hence, there was no significant benefit of dual antiplatelet therapy in this patient population and in fact, there is evidence that this combination leads to increased adverse events [49].
The question of whether a short-term use of aggressive, dual antiplatelet therapy in patients with acute minor stroke or TIA prevents recurrent stroke has been addressed in one large randomized clinical trial. The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial randomized over 5000 Chinese patients with acute TIA or minor stroke to receive either clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day for the first 21 days or placebo. Both groups received aspirin 75 mg/day for a 3-month period. Patients were randomized within 24 hours after TIA or stroke. The primary efficacy endpoint was any recurrent stroke (ischemic or hemorrhagic) at 3 months. The results of the trial were recently presented at the International Stroke Conference in February, 2013. The dual antiplatelet group had a significantly lower rate of any recurrent stroke (hazard ratio 0.68). The recurrent ischemic stroke rate was also significantly lower in the dual antiplatelet group compared to aspirin alone (7.9% versus 11.4%, ARR 3.5%). The brain hemorrhage rates were surprisingly low with both groups having a rate of only 0.3% [50, 51].

A similar North American trial called the Platelet Oriented Inhibition in New TIA and ischemic stroke (POINT) trial is currently underway. The POINT trial has a shorter randomization window compared with CHANCE (12 hours vs. 24 hours) and a higher loading dose of clopidogrel (600 mg vs. 300 mg) [52].

Patients with TIA or ischemic stroke should receive an antiplatelet agent. Short-term use of aggressive, dual antiplatelet therapy may be considered in patients with acute minor stroke or TIA.

### Anticoagulation in cerebral ischemia due to cardiac embolism

- Patients with a high-risk cardiac source of embolism, in particular atrial fibrillation (AF), should typically be treated with oral anticoagulation. Options for patients with AF include dose-adjusted warfarin (INR 2.0 to 3.0), dabigatran, rivaroxaban, and apixaban.
- Patients with contraindications or unwilling to use oral anticoagulation should receive ASA 81–325 mg/day.
- Patients with mechanical heart valves should be anticoagulated with an INR between 2.0 and 3.5, depending upon the valve.
- Patients with biological heart valves are anticoagulated for 3 months.
- In patients with TIA or minor stroke, oral anticoagulation can be initiated immediately after the exclusion of cerebral hemorrhage.
- The combination of ASA plus clopidogrel is inferior to oral anticoagulation with warfarin and carries a similar bleeding risk.
- There is no evidence that the use of anticoagulation in patients with low left ventricular ejection fraction is superior to antiplatelet therapy.

The evidence that oral anticoagulation prevents recurrent strokes in patients with AF results from the European Atrial Fibrillation Trial [53]. This randomized placebo-controlled trial showed a 68% RRR for a recurrent stroke for patients treated with warfarin compared to only 19% for patients receiving 300 mg ASA. Numbers needed to treat (NNT) are 12/year [53]. Therefore, oral anticoagulation in patients with AF is by far the most effective treatment for secondary stroke prevention. A Cochrane analysis concluded that oral anticoagulation is more effective than ASA for the prevention of vascular events (odds ratio [OR] 0.67; 95% CI 0.50–0.91) or recurrent stroke (OR 0.49; 95% CI 0.33–0.72) [54]. The risk of major bleeding complications is significantly increased but not the risk of intracranial bleeds. Patients with intermittent AF have a similar stroke risk to patients with
permanent AF [55, 56]. The optimal INR range for oral anticoagulation is between 2.0 and 3.0 [57]. INR values >3.0 lead to an increased risk of major bleeding complications in particular in the elderly [58].

The ACTIVE study compared the combination of ASA and clopidogrel versus oral anticoagulation with warfarin in patients with AF [59]: the study was terminated prematurely due to a significant reduction of stroke and systemic embolism in favor of warfarin. The rate of major bleeding complications was not different between the two regimens.

More recently, several newer oral anticoagulants have become available as an alternative to dose-adjusted warfarin in non-valvular AF. Currently, three agents have been approved for use by the United States Food and Drug Administration (FDA): dabigatran, rivaroxaban, and apixaban. These three agents have all been studied in large clinical trials.

Dabigatran is a direct thrombin inhibitor, which was compared with warfarin in the RE-LY trial. In RE-LY, 18 113 patients were randomly assigned to receive dabigatran 150 mg twice a day, dabigatran 110 mg twice a day, or dose-adjusted warfarin. Patients were followed for a mean of 2.0 years. The primary outcome was hemorrhagic stroke, ischemic stroke, or systemic embolism. The 150 mg dabigatran group had a significantly lower rate of the primary outcome compared with the warfarin group (1.11% per year for dabigatran versus 1.69% per year for warfarin, p ≤ 0.001 for superiority) and had a similar rate of major bleeding (3.11% per year for dabigatran versus 3.36% per year in the warfarin group, p = 0.31). The 110 mg dabigatran group had a similar rate of the primary outcome compared with warfarin (1.53% per year for dabigatran versus 1.69% per year for warfarin, p < 0.001 for noninferiority) but had a lower risk of hemorrhagic stroke (2.71% per year for dabigatran versus 3.36% per year for warfarin) [60].

Rivaroxaban, a factor X inhibitor, was compared with warfarin in the ROCKET AF trial. In the trial, 14 264 patients with non-valvular AF and at increased risk for stroke were randomized to receive either rivaroxaban 20 mg daily or dose-adjusted warfarin. The primary endpoint was hemorrhagic stroke, ischemic stroke, or systemic embolism. The median follow-up was 1.9 years. In the intention-to-treat analysis, the rate of the primary endpoint was 2.1% per year for the rivaroxaban group compared with 2.4% per year in the warfarin group (p < 0.001 for noninferiority). The rate of major and non-major clinically relevant bleeding was not significantly different between the two groups (14.9% per year for rivaroxaban versus 14.5% per year for warfarin, p = 0.44) [61].

The ARISTOTLE trial compared another factor X inhibitor, apixaban, with warfarin. The trial randomized 18 201 patients with AF and at least one additional stroke risk factor to either apixaban 5 mg twice a day or dose-adjusted warfarin. The primary outcome was a combination of hemorrhagic stroke, ischemic stroke, or systemic embolism. The median follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group versus 1.60% per year in the warfarin group (p ≪ 0.001 for noninferiority and p = 0.01 for superiority). The rate of major bleeding was lower in the apixaban group compared to the warfarin group: 2.13% per year for apixaban and 3.09% per year for warfarin (p < 0.001) [62].

The AVERROES trial evaluated apixaban 5 mg twice daily versus aspirin 81–324 mg daily in patients with AF and increased risk of stroke that were felt to be unsuitable for vitamin K antagonist therapy. Patients were followed for a mean of 1.1 years for the primary outcome of stroke (hemorrhagic or ischemic) or systemic embolism. The study was terminated early as recommended by the data safety monitoring board because of a clear benefit in favor of apixaban [63].

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial was designed to determine whether anticoagulation was superior to antiplatelet therapy in patients with heart failure and low left ventricular ejection fraction. The trial randomized 2305 patients to either dose-adjusted warfarin with a target INR range of 2.0–3.5 or aspirin 325 mg daily. The mean follow-up was 3.5 years and the primary outcome a composite endpoint of ischemic stroke, intracerebral hemorrhage, or death from any cause. The rate of the primary outcome was not significantly different between the two groups: 7.47 events per 100 patient-years in the warfarin group and 7.93 in the aspirin group (p = 0.40). The warfarin group had a lower rate of ischemic stroke compared to aspirin: 0.72 events per 100 patient-years for warfarin versus 1.36 per 100 patient-years for aspirin (p = 0.005). However, as expected, the rate of major hemorrhage was higher in the warfarin group: 1.78 events per 100 patient-years for warfarin as opposed to 0.87 for aspirin (p < 0.001) [64].
At present there are no prospectively collected data as to when it is safe to initiate oral anticoagulation after a TIA or ischemic stroke. Patients with acute ischemic events were excluded from the trials with the novel anticoagulants. The recommendation is to start anticoagulation in patients with TIA on day 1, in patients with mild strokes on day 3, and in patients with moderate strokes on day 6. In patients with severe stroke anticoagulation can be initiated after 2 weeks provided that a repeat CT does not show major hemorrhagic transformation.

Patent foramen ovale closure

Autopsy and imaging studies have shown that patent foramen ovale (PFO) occurs in about 25% of the normal population but PFOs can be detected in up to 44% of younger stroke patients [65, 66]. Recently, there have been three clinical, randomized trials of PFO closure versus medical management alone.

The first trial to be published was the Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale (CLOSURE) trial, which randomized 980 patients between the ages of 18 and 60 with cryptogenic stroke or TIA in the previous 6 months to PFO closure versus medical management alone. The primary endpoint was a composite of stroke or transient ischemic attack during 2 years of follow-up, death from any cause during the first 30 days, or death from neurological causes between 31 days and 2 years. There was no significant difference between the two groups; 5.5% of the surgical group had a primary endpoint event vs. 6.8% of the medical group (p = 0.37) [67].

The Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke (RESPECT) trial randomized 414 patients age 18 to 60 with ischemic stroke, TIA, or a peripheral thromboembolic event and a PFO to either PFO closure or medical management alone. The primary endpoint was a composite of death, non-fatal stroke, TIA, or peripheral embolism. The primary endpoint was not significantly different in the two groups with 3.4% of closure patients and 5.2% of medical patients experiencing a primary endpoint after a mean follow-up of 4 years [69].

In summary, none of the three clinical trials demonstrated that PFO closure was significantly better than medical management in patients with cryptogenic stroke or TIA and the rate of recurrent stroke was low in all three studies. Therefore, in general, PFO patients should be managed medically. However, as trends favoring closure were noted in all three studies, PFO closure may be considered for highly selected patients such as individuals with recurrent cryptogenic stroke despite medical management [67–69].

Patent foramen ovale (PFO) closure should not be recommended as first-line treatment in patients with cryptogenic stroke. PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical management.

Anticoagulation in cerebral ischemia of non-cardiac origin

- Oral anticoagulation is not superior to ASA and is not recommended.
- The benefit of anticoagulation for patients with dissection of the vertebral or carotid arteries versus antiplatelet drugs has not been studied in head-to-head trials.
- Patients with cryptogenic stroke and coagulation disorders, e.g. protein C or S deficiency or factor V (Leiden) mutation, may benefit from oral anticoagulation. The optimal treatment duration and specific coagulation disorders that warrant anticoagulation are not clear.
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 a cardiac source of embolism [70]. 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) had a similar rate of ischemic events and bleeding complications comparing warfarin (INR 1.4–2.8) and ASA in stroke patients without a cardiac source of embolism [71]. This result was replicated in the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) study [72]. ESPRIT found a lower rate of ischemic events with anticoagulation counterbalanced by an increased risk of intracranial bleeds.

A Cochrane analysis of five trials, with 4076 patients, was unable to show that anticoagulants are 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 relative risk of major bleeding complications for low-intensity anticoagulation was 1.27 (95% CI 0.79–2.03) 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) [73].

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 [74]. There was in addition no difference in event rates between patients positive or negative for aPL. The evidence for anticoagulation in patients with protein C, protein S, or antithrombin deficiency is derived from patients with deep vein thrombosis and not from patients with stroke.

The possible benefit of oral anticoagulation, compared with antiplatelet drugs, for the long-term treatment of dissections has never been studied in a randomized trial. 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 of 15%. The event rate in patients with anticoagulation was 8.3% and in patients receiving ASA 12.4%; the difference was not statistically significant [75]. A Cochrane review of 26 observational studies in 327 patients found no difference between anticoagulation and antiplatelet drugs for the endpoints death and severe disability [76]. A more recent review came to a similar conclusion [77].

**Section 4: Therapeutic strategies and neurorehabilitation**

**Carotid endarterectomy and stenting with balloon angioplasty**

- Symptomatic patients with significant stenosis of the internal carotid artery (ICA) should undergo carotid endarterectomy. The benefit of surgery increases with the degree of stenosis between 70% and 95%. The benefit of surgery is highest in the first 2–4 weeks after the initial TIA or minor stroke.
- The benefit of surgery is no longer present when the complication rate exceeds 6%.
- Patients should receive ASA prior to, during, and after endarterectomy. Clopidogrel should be replaced by ASA 5 days before surgery.
- At present carotid stenting has a slightly higher short-term complication rate and similar medium-term outcomes. The use of protection systems does not decrease the complication rate. The restenosis rate is higher after stenting. Whether this translates into higher long-term event rates is not yet known. The complication rate of carotid stenting is age dependent and increases beyond the age of 65–68 years.
- The combination of clopidogrel (75 mg) plus ASA (75–100 mg) is recommended in patients after carotid stenting for 1–3 months based on extrapolation from studies of coronary stents.

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 [78–84]. Taken together the trials found an ARR of 13.5% over 5 years for the combined endpoint of stroke and death in favor of carotid endarterectomy [84]. The risk reduction is even higher in stenosis >90%. In patients with 50–69%
ICA stenosis the 5-year ARR for the endpoint ipsilateral stroke is 4.6%. This benefit is mainly seen in males. 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 [85].

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 a >50% stenosis (NASCET criteria) or >70% (ESC criteria) within 6 months after TIA or minor stroke to carotid endarterectomy or stenting [86]. 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 on. A post-hoc subgroup analysis identified age <68 years as a factor in a lower complication rate in patients treated with stenting. The complication rate of surgery was not age dependent [87]. The use of a 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 favoring carotid surgery (9.6% vs. 3.9%; OR 2.5; 95% CI 1.25–4.93) [88]. Taken together the results of the two studies show a lower complication rate for endarterectomy [89]. The reported medium-term outcomes were comparable and the restenosis rate was higher after carotid stenting.

The CREST trial compared stenting versus endarterectomy for the treatment of carotid artery stenosis (CAS). Patients who were either symptomatic or asymptomatic were included in the study. Patients were considered symptomatic if they experienced a TIA, amaurosis fugax, or minor non-disabling stroke in the territory of the study carotid artery within 180 days prior to randomization. Symptomatic patients were required to have stenosis of 50% or more on angiography, 70% or more on ultrasonography, or 70% or more on computed tomographic angiography or magnetic resonance angiography. The primary endpoint was a composite of either (1) stroke, myocardial infarction, or death from any cause during the periprocedural period or (2) any ipsilateral stroke within 4 years after randomization. The study followed 2502 patients for a median follow-up period of 2.5 years. The estimated 4-year rate of the primary endpoint was not significantly different between the two groups (7.2% for stenting and 6.8% for endarterectomy, p = 0.51). However, there was a difference in the periprocedural risk of stroke and myocardial infarction between the two groups. The rate of periprocedural stroke was higher in the stenting group (4.1% for stenting versus 2.3% for endarterectomy, p = 0.01) whereas the risk of periprocedural myocardial infarction was higher in the endarterectomy group (1.1% for stenting versus 2.3% for endarterectomy, p = 0.03). The rate of ischemic stroke after the periprocedural period was similar between the groups (2.0% and 2.4%, respectively; p = 0.85). Lastly, there was a significant relationship between age and treatment efficacy (p = 0.02): patients <70 tended to do better with stenting whereas those >70 did better with endarterectomy [90].

Symptomatic patients with significant stenosis of the internal carotid artery (ICA) should undergo carotid endarterectomy. Carotid artery stenting is a reasonable alternative to endarterectomy in patients who are deemed to be unsuitable or at high risk for endarterectomy.

**Intracranial stenosis**

- Symptomatic patients with intracranial stenosis or occlusions should be treated with antiplatelet therapy.
- In patients with recurrent events, angioplasty can be considered.

The WASID-II study recruited 569 patients with intracranial stenosis and randomized them to either oral anticoagulation (INR 2.0–3.0) or ASA (1300 mg/day). The study was terminated prematurely due to a higher rate of bleeding complications with warfarin [91]. Therefore ASA is recommended in these patients. Whether the high dose of ASA is needed is not known. Lower doses are better tolerated and appear to have equal efficacy in other ischemic stroke etiologies. Predictors for a recurrent ischemic event were the degree of stenosis, stenosis in the
Coronary artery disease, vertebrobasilar system, and female sex [92]. In patients with recurrent ischemic events stenting might be considered [93, 94], although not based on the results of randomized trials.

The Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial randomized patients with recent TIA or stroke due to high-grade intracranial stenosis (70–99%) to aggressive medical management alone or aggressive medical management plus stenting. The primary endpoint was either (1) stroke or death within 30 days after enrollment or after a revascularization procedure, or (2) stroke in the territory of the qualifying artery beyond 30 days. Enrollment was stopped early after 451 patients were randomized because the 30-day rate of stroke or death was 14.7% in the stenting arm and only 5.8% in the medical-management group (p = 0.002). One year rates of the primary endpoint were 20.0% in the stenting group and 12.2% in the medical-management group. Given the significantly higher stroke rates in the stenting arm, patients with TIA or stroke due to intracranial stenosis should typically be managed with medical therapy alone. If recurrent stroke or TIA events occur in the distribution of the stenotic intracranial vessel despite optimal medical management, then angioplasty (preferably without stenting) may be considered. However, there are no randomized clinical trials comparing medical management alone with medical management and angioplasty without stenting in patients with intracranial stenosis [95].

**Chapter summary**

- **Antihypertensive therapy** reduces the risk of stroke. Most likely all antihypertensive drugs are effective in secondary stroke prevention. More important than the choice of a class of antihypertensives is to achieve the systolic and diastolic blood pressure targets (<140/90 mmHg in non-diabetics and <130/80 mmHg in diabetics). In many cases this requires combination therapy and lifestyle modification.
- **Statin** therapy reduces the rate of recurrent stroke and vascular events. The target range of LDL is 70–100 mg/dl.
- Aggressive lowering of **blood glucose** does not reduce the risk of stroke and might even increase mortality.

- **Treatment of increased plasma levels of homocysteine** with vitamin B6, vitamin B12, and folic acid is not effective in secondary stroke prevention.
- **Hormone replacement** after menopause is not effective in the secondary prevention of stroke and may even increase the risk of fatal strokes.
- Patients with **TIA or ischemic stroke** should receive antiplatelet drugs. The choices are acetylsalicylic acid (ASA 50–150 mg), the combination of ASA (2 × 25 mg) and extended-release dipyridamole (ER-DP 2 × 200 mg) or clopidogrel (75 mg). Short-term use of aggressive, dual antiplatelet therapy may be considered in patients with acute minor stroke or TIA.
- Patients with a **cardiac source of embolism**, in particular atrial fibrillation (AF), should be treated with oral anticoagulation. Options for patients with AF include dose-adjusted warfarin (INR 2.0–3.0), dabigatran, rivaroxaban, and apixaban. Patients with contraindications or unwilling to use oral anticoagulation should receive ASA 100–300 mg/day.
- In cerebral ischemia of **non-cardiac** origin oral anticoagulation is not superior to ASA and is not recommended.
- Patent foramen ovale (PFO) closure should not be recommended as first-line treatment in patients with cryptogenic stroke. PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical management.
- Symptomatic patients with significant **stenosis** of the internal carotid artery (ICA) (degree of stenosis between 70% and 95%) should undergo carotid endarterectomy. Carotid artery stenting is a reasonable alternative to endarterectomy in patients who are deemed to be unsuitable or at high risk for endarterectomy. Patients should receive ASA prior to, during, and after endarterectomy or the combination of clopidogrel (75 mg) plus ASA (75–100 mg) after carotid stenting for 1–3 months.
- Symptomatic patients with **intracranial stenosis** or occlusions should be treated with optimal medical management, which includes antiplatelet therapy and high-dose statins (if deemed appropriate). In patients with recurrent events, angioplasty can be considered.
Chapter 22: Secondary prevention

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