Chapter 24
Secondary Prevention
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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]. 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 [2, 3]. 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 [4].

Immediate evaluation of patients with stroke or TIA, identification of the pathophysiology, and initiation of pathophysiology-based treatment is of major importance [2, 5]. In the following sections, we will deal with the treatment of risk factors, anti-thrombotic therapy, and surgery or stenting of significant stenosis of extracranial arteries. Each paragraph will be introduced by recommendations, followed by the scientific justification.

Treatment of Risk Factors

Hypertension

- Anti-hypertensive therapy reduces the risk of stroke. The combination of angiotensin-converting enzyme (ACE) inhibitors with a diuretic is more effective than placebo.
- Angiotensin-receptor blockers (ARBs) are more effective than calcium-channel blockers. Ramipril reduces vascular events in patients with vascular risk factors. Most likely all anti-hypertensive 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 anti-hypertensive is to achieve the systolic and diastolic blood pressure targets (<140/90 mmHg in non-diabetics and <130/80 mmHg in diabetics). The new target promoted by ACC/AHA of systolic blood pressure <130 mmHg applies for primary stroke prevention. 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.

Few studies investigated the efficacy of classes of anti-hypertensive 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 included patients with vascular risk factors even with normal blood pressure under the assumption that end organs such as the brain will be protected [6]. A meta-analysis from 2003 comprised seven studies of 15 527 patients with TIA, or ischemic or hemorrhagic stroke, who were followed for 2–5 years. Treatment with anti-hypertensives 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% [7]. 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%). A more recent pairwise meta-analysis with 42 736 patients on anti-hypertensive treatment compared to placebo lowered the risk for recurrent stroke with a risk ratio of 0.73 (95% confidence interval [CI] 0.62–0.87). Systolic blood pressure was linearly related to lower risk of recurrent stroke [8].

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 [9].

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was the first large-scale trial specifically performed in patients after stroke [10]. Patients (n = 6105) were treated with perindopril as monotherapy or in combination with indapamide (a diuretic) 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%.

The Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipin for Secondary Prevention (MOSES) study included 1352 patients with hypertension who had suffered a stroke in the previous 24 months [11]. Patients were treated either with eprosartan (600 mg) or with nitrendipine (10 mg) on top of additional anti-hypertensive 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 20332 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 [12]. Telmisartan did not significantly lower the rate of recurrent strokes, other major vascular events, or new diabetes.

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. 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 [13].

In summary, anti-hypertensive therapy reduces the risk of ischemic and hemorrhagic stroke. Most likely all anti-hypertensive drugs are effective in secondary stroke prevention. The optimal blood pressure target for secondary stroke prevention (<140 mmHg) and the most favorable timing for achieving this goal after the event remain unknown. 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 possible benefit of PCSK9 inhibitors has not yet been shown for secondary stroke prevention.

The association of cholesterol levels and the risk of recurrent stroke is not as strong as the association with the risk of MI. Statins lower the risk of stroke in patients with CHD. The RRR calculated from a meta-analysis is 21% [14]. The AACE 2017 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 [15].

Patients with stroke without CHD were investigated in a subgroup of the Heart Protection Study (HPS). Within the HPS patient population of 20536 high-risk patients, 3280 patients had TIA or stroke, 1820 of them without concomitant CHD. The RRR achieved by 40 mg simvastatin given for 5 years for vascular events was 20% and the ARR 5.1% [16]. 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 [17]. 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 [18]. Patients received either 80 mg atorvastatin or placebo. After an average of 4.9 years the primary endpoint
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The rate of ischemic stroke was reduced (218 vs. 274), whereas hemorrhagic strokes were more frequent with atorvastatin (55 vs. 33). Recently PCSK9 inhibitors were introduced to treat hypercholesterolemia. The number of patients with stroke included in these studies and the number of recurrent strokes was small. Therefore, the possible benefit of PCSK9 inhibitors at present is unclear, but may be shown in the ongoing large endpoint trials [19].

Therapy with a statin should be initiated early after an ischemic stroke or TIA. The discontinuation of a statin in patients with a stroke or acute coronary syndrome might be associated with higher morbidity and mortality [20, 23, 24]. 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 and Insulin Resistance

Aggressive lowering of blood glucose in patients with diabetes mellitus does not reduce the risk of stroke and might even increase mortality [21]. In a meta-analysis of three randomized controlled trials with 4,980 participants use of pioglitazone in stroke patients with insulin resistance, pre-diabetes, and diabetes mellitus was associated with lower risk of recurrent stroke (hazard ratio [HR] 0.68; 95% CI 0.50–0.92; p = 0.01) and future major vascular events (HR 0.75; 95% CI 0.64–0.87; p = 0.0001) [22]. Empagliflozin reduces the risk of death due to heart failure, but does not reduce the risk of stroke [23]. Therefore, treatment of diabetes mellitus should not be restricted to drug treatment only, 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. Vitamin B12 might be effective in stroke patients with normal renal function.

The VISP study was unable to show a benefit of the treatment of high homocysteine in stroke patients with B vitamins and folic acid [24]. The HOPE-2 study also failed to demonstrate benefit [25]. The study included 5,522 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. A post-hoc meta-analysis, however, indicated that stroke patients with normal renal function might benefit from substitution of B vitamins [26].

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 [27]. Therefore, in general, hormone replacement after menopause should be avoided following a stroke.

Anti-Platelet Therapy

- Patients with TIA or ischemic stroke should receive anti-platelet 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.
- Ticagrelor is not superior to aspirin in patients with TIA or minor stroke for prevention of the combination of stroke, myocardial infarction, or death, but may be superior for prevention of ischemic stroke.
• The efficacy of anti-platelet 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 anti-platelet therapy the recurrence risk should be evaluated and the anti-platelet therapy adapted to the new risk. There is no evidence that changing anti-platelet 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 after stenting of the carotid or vertebral arteries.

• In patients with lacunar stroke, there is no significant benefit of dual anti-platelet therapy with clopidogrel plus aspirin over aspirin alone. The combination increases the risk of hemorrhagic side-effects. Anti-platelet 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 [28–30]. The RRR for non-fatal stroke achieved by anti-platelet therapy in patients with TIA or stroke is 23% (reduced from 10.8% to 8.3% in 3 years) [29]. 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 an RRR of 13% (95% CI 6–19) for the combined endpoint of stroke, MI, and vascular death [31]. The highest benefit of aspirin is in the early phase after the initial TIA or ischemic stroke [32]. In a pooled analysis of 15 778 participants from 12 trials of aspirin versus control in secondary prevention, aspirin reduced the 6-week risk of recurrent ischemic stroke by about 60% (84 of 8 452 participants in the aspirin group had an ischemic stroke vs. 175 of 7 326; HR 0.29), with greatest benefit noted in patients presenting with TIA or minor stroke. There is no relationship between the dose of ASA and its efficacy in secondary stroke prevention [31, 33]. 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 [34, 35]. Gastrointestinal bleeding complications in the elderly on aspirin can be prevented by proton pump inhibitors [36]. Clopidogrel monotherapy (75 mg/day) was compared to ASA (325 mg/day) in 19 185 patients with stroke, MI, or PAD in the CAPRIE trial [37]. The combined endpoint of stroke, MI, and vascular death showed an RRR of 8.7% in favor of clopidogrel. The ARR was 0.51%. The highest benefit of clopidogrel was seen in patients with PAD. The risks of gastrointestinal bleeds (1.99% vs. 2.66%) and gastrointestinal side-effects (15% vs. 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 [38] and failed to show the superiority of combination anti-platelet therapy for the combined endpoint of stroke, MI, vascular death, and hospitalization due to a vascular event. The combination of aspirin and clopidogrel resulted in a significant increase in bleeding complications, and therefore is not recommended for long-term secondary stroke prevention.

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 [39]. Similarly to MATCH, the study failed to show a benefit of combination therapy and displayed a higher bleeding rate with the combination of aspirin and clopidogrel. Symptomatic patients, however, showed a trend towards a benefit for combination anti-platelet therapy [40].

The combination of low-dose ASA and ER-DP was investigated in the second European Stroke Prevention Study (ESPS2) with 6 602 patients with TIA or stroke [41]. 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 [42]. The industry-independent ESPRIT study [43] randomized 2 739 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 an 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 an RRR of 18% (95% CI 9–26) in favor of the combination for the combined vascular endpoint [43].

A head-to-head comparison of clopidogrel and ASA + ER-DP was performed in the PROFESS study [44]. 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 24.1 gives an overview of ARR and RRR for different approaches in secondary stroke prevention.

Glycoprotein (GP)-IIb/IIIa receptor antagonists are effective in the acute coronary syndrome. Oral GP-IIb/IIIa antagonists are not superior to ASA and carry a higher bleeding risk as shown in the BRAVO trial [34].

Ticagrelor was compared to aspirin in 13 199 patients with a non-severe ischemic stroke or high-risk transient ischemic attack [45]. Patients received either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2–90) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2–90). During the 90 days of treatment, stroke, myocardial infarction, or death occurred in 442 of the 6 589 patients (6.7%) treated with ticagrelor, versus 497 of the 6 610 patients (7.5%) treated with aspirin (HR 0.89; 95% CI 0.78–1.01, p = 0.07). The main secondary endpoint, ischemic stroke, occurred in 385 patients (5.8%) in the ticagrelor group and 441 patients (6.7%) in the aspirin group (HR 0.87; 95% CI 0.71–1.07).

### Table 24.1 Strategies for prevention of recurrent stroke after an initial TIA or ischemic 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>Anti-hypertensive 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 ischemic stroke</td>
<td>18–22%</td>
<td>1.3%</td>
<td>77</td>
<td>ASA doses &gt;150 mg ¼ higher bleeding risk</td>
</tr>
<tr>
<td>ASA 50 mg + dipyridamole 400 mg versus ASA</td>
<td>23%</td>
<td>1.0–1.5%</td>
<td>33–100</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>Oral anti-coagulation in cardiac source of embolism (AF) INR 2.0–3.0</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>

Notes: * Outcome stroke and death.

NNT = number needed to treat; RR = risk reduction; AF = atrial fibrillation; INR = international normalized ratio.
CI 0.76–1.00; p = 0.046). Major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3%, respectively, and fatal bleeding in 0.1% and 0.1%. In the SOCRATES study ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death; however, there was a significant reduction in ischemic stroke. Long-term prevention with trifusal, terutroban, and voraxapar is either not superior or has a higher bleeding risk compared to aspirin [46].

The use of dual anti-platelet therapy in patients with lacunar stroke was investigated in the SPS3 trial, which randomized 3 020 patients with recent, MRI-confirmed symptomatic lacunar strokes into two anti-platelet groups: aspirin 325 mg daily and clopidogrel 75 mg daily versus aspirin 325 mg daily and placebo [47]. 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 anti-platelet 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 anti-platelet therapy in this patient population and, in fact, there is evidence that this combination leads to increased adverse events.

The question of whether a short-term use of aggressive, dual anti-platelet therapy in patients with acute minor stroke or TIA prevents recurrent stroke has been addressed in a randomized clinical trial in China. The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial randomized over 5 000 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 [48]. 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 dual anti-platelet group had a significantly lower rate of any recurrent stroke (HR 0.68). The recurrent ischemic stroke rate was also significantly lower in the dual anti-platelet group compared to aspirin alone (7.9% vs. 11.4%, ARR 3.5%). The brain hemorrhage rates were surprisingly low, with both groups having a rate of only 0.3%.

Patients with TIA or ischemic stroke should receive aspirin, clopidogrel, or aspirin plus extended-release dipyridamole. Short-term use of dual anti-platelet therapy in patients with acute minor stroke or TIA and high risk of recurrence.

## Anti-Coagulation in Cerebral Ischemia due to Cardiac Embolism

- Patients with a high-risk cardiac source of embolism, in particular atrial fibrillation (AF), should be treated with oral anti-coagulation. Options for patients with AF include dose-adjusted warfarin (INR 2.0–3.0) or the non-vitamin K oral anti-coagulants (NOACs) apixaban, dabigatran, edoxaban, or rivaroxaban.
- Patients with contraindications or unwilling to use oral anti-coagulation should receive ASA 81–325 mg/day [49]. Patients with mechanical heart valves should be anti-coagulated with an INR between 2.0 and 3.5, depending upon the valve. NOACs are contraindicated in patients with moderate to severe mitral stenosis or rheumatic heart disease, or in patients with mechanical heart valves.
- Patients with biological heart valves are anti-coagulated for 3 months.
- In patients with TIA or minor stroke, oral anti-coagulation can be initiated immediately after the exclusion of cerebral hemorrhage.
- The combination of ASA plus clopidogrel is inferior to oral anti-coagulation with warfarin and carries a similar bleeding risk.
- There is no evidence that the use of anti-coagulation in patients with low left ventricular ejection fraction is superior to anti-platelet therapy.

The evidence that oral anti-coagulation prevents recurrent strokes in patients with AF results from the European Atrial Fibrillation Trial [50]. This randomized placebo-controlled trial showed a 68% RRR for recurrent stroke in patients treated with warfarin compared to only 19% for patients receiving 300 mg ASA. Numbers needed to treat are 12 per year [50]. Therefore, oral anti-coagulation in patients with AF is by far the most effective treatment for secondary stroke prevention. A Cochrane analysis concluded that oral
anti-coagulation with warfarin 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) [51]. 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 [52]. The optimal INR range for oral anticoagulation is between 2.0 and 3.0 [49]. INR values >3.0 lead to an increased risk of major bleeding complications, in particular in the elderly [53].

The ACTIVE study compared the combination of ASA and clopidogrel versus oral anticoagulation with warfarin in patients with AF [54]: 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 treatment regimens.

Since 2009, four NOACs have become available as an alternative to dose-adjusted warfarin in non-valvular AF: apixaban, dabigatran, edoxaban, and rivaroxaban.

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 daily, dabigatran 110 mg twice daily, or dose-adjusted warfarin [55]. 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 vs. 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 vs. 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 vs. 1.69% per year for warfarin, p <0.001 for non-inferiority), but had a lower risk of hemorrhagic stroke (2.71% per year for dabigatran vs. 3.36% per year for warfarin).

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 [56]. 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 non-inferiority). The rate of major and non-major clinically relevant bleeding was not significantly different between the two groups (14.9% per year for rivaroxaban vs. 14.5% per year for warfarin, p = 0.44).

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 [57]. 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 non-inferiority 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).

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 [58]. 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.

ENGAGE-AF was a randomized, double-blind, double-dummy trial comparing two once-daily regimens of edoxaban with warfarin in 21 105 patients with moderate-to-high risk of atrial fibrillation [59]. The annualized rate of the primary endpoint (stroke or systemic embolism) during treatment was 1.50% with warfarin, as compared with 1.18% with high-dose edoxaban (HR 0.79; 97.5% CI 0.63–0.99) and 1.61% with low-dose edoxaban (HR 1.07; 97.5% CI 0.87–1.31). In the intention-to-treat analysis, there was a trend favoring high-dose edoxaban versus warfarin (HR 0.87; 97.5% CI 0.73–1.04; p = 0.08) and an unfavorable trend with low-dose edoxaban versus warfarin (HR 1.13; 97.5% CI 0.96–1.34; p = 0.10). The annualized rate of major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban (HR 0.80; 95% CI 0.71–0.91; p <0.001) and 1.61% with low-dose edoxaban (HR 0.47; 95% CI 0.41–0.55; p <0.001).

All studies comparing NOACs with warfarin had a subgroup of AF patients with a prior TIA or stroke.
In contrast to the patients included in the overall trials, patients with a prior TIA or stroke were comparable in terms of risk factors and concomitant diseases at baseline. In 20 500 patients, compared to warfarin, non-vitamin K antagonist oral anticoagulants were associated with a significant reduction of stroke/systemic embolism (RRR 13.7%, ARR 0.78%, NNT 127), hemorrhagic stroke (RRR 50.0%, ARR 0.63%, NNT 157), any stroke (RRR 13.1%, ARR 0.7%, NNT 142), and intracranial hemorrhage (RRR 46.1%, ARR 0.88%, NNT 113) over 1.8–2.8 years [60]. Therefore, NOACs should be preferred over warfarin in secondary stroke prevention in patients with AF.

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial was designed to determine whether anti-coagulation was superior to anti-platelet therapy in patients with heart failure and low left ventricular ejection fraction [61]. The trial randomized 2 305 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).

At present, there are only few data as to when it is safe to initiate oral anti-coagulation after a TIA or ischemic stroke [62–64]. Patients with acute ischemic events were excluded from the trials with the novel anti-coagulants. A common recommendation is to start anti-coagulation 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 anti-coagulation can be initiated after 2 weeks provided that a repeat CT does not show major hemorrhagic transformation [49].

Patients with a cardiac source of embolism, in particular atrial fibrillation, should be treated with oral anti-coagulation. Options include dose-adjusted warfarin (INR 2.0–3.0), apixaban, dabigatran, edoxaban, and rivaroxaban.

**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]. Until recently three clinical, randomized trials of PFO closure versus medical management alone in patients with cryptogenic stroke were negative. The Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale (CLOSURE) trial randomized 909 patients between the ages of 18 and 60 with cryptogenic stroke or TIA 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 versus 6.8% of the medical group (p = 0.37) [66].

The Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke (RESPECT) trial randomized 980 patients of ages 18 to 60 with ischemic stroke or TIA in the prior 6 months to PFO closure versus medical management alone. The primary results of the trial were analyzed after 25 primary endpoints occurred. The primary endpoint was defined as a composite of stroke or TIA 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. In the intention-to-treat (ITT) analysis, nine events occurred in the closure group versus 16 in the medical group. There was no significant difference between the two groups in the ITT analysis (hazard ratio with closure 0.49; 95% CI 0.22–1.11, p = 0.08) [67].

The Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism trial (PC-Trial) randomized 414 patients aged 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 [68].

Three more recent trials with a longer duration of follow-up showed a significant benefit of PFO closure in patients <60 years of age with cryptogenic stroke. CLOSE was a multicenter, randomized, open-label trial. Patients 16–60 years of age...
age who had had a recent stroke attributed to PFO, with an associated atrial septal aneurysm or large interatrial shunt, were randomized to transcatheter PFO closure plus long-term anti-platelet therapy (PFO closure group), anti-platelet therapy alone (anti-platelet-only group), or oral anti-coagulation (anti-coagulation-only group) [69]. The primary outcome was occurrence of stroke. A total of 663 patients underwent randomization and were followed for a mean (+/−SD) of 5.3+/−2.0 years. No stroke occurred among the 238 patients in the PFO closure group, whereas stroke occurred in 14 of the 235 patients in the anti-platelet-only group (HR 0.03; 95% CI 0–0.26; p <0.001). Procedural complications from PFO closure occurred in 14 patients (5.9%). The number of serious adverse events did not differ significantly between the treatment groups (p = 0.56). In the comparison of oral anti-coagulation alone with anti-platelet therapy alone, stroke occurred in 3 of 187 patients assigned to oral anti-coagulants and in 7 of 174 patients assigned to anti-platelet therapy alone (no statistical analysis performed because of inadequate power).

The Gore REDUCE study investigated the effect of PFO closure combined with anti-platelet therapy versus anti-platelet therapy alone on the risks of recurrent stroke and new brain infarctions [70]. The multinational trial recruited patients with a PFO who had had a cryptogenic stroke. Patients were randomly assigned in a 2:1 ratio, to undergo PFO closure plus anti-platelet therapy (PFO closure group) or to receive anti-platelet therapy alone (anti-platelet-only group). The co-primary endpoints were freedom from clinical evidence of ischemic stroke within at least 24 months after randomization and the 24-month incidence of new brain infarction, which was a composite of clinical ischemic stroke or silent brain infarction detected on imaging. The study enrolled 664 patients of whom 81% had moderate or large interatrial shunts. During a median follow-up of 3.2 years, clinical ischemic stroke occurred in 6 of 441 patients (1.4%) in the PFO closure group and in 12 of 223 patients (5.4%) in the anti-platelet-only group (HR 0.23; 95% CI 0.09–0.62; p = 0.002). The incidence of new brain infarctions was significantly lower in the PFO closure group than in the anti-platelet-only group (22 patients [5.7%] vs. 20 patients [11.3%]; RR 0.51; 95% CI 0.29–0.91; p = 0.04), but the incidence of silent brain infarction did not differ significantly between the study groups (p = 0.97). Serious adverse events occurred in 23.1% of the patients in the PFO closure group and in 27.8% of the patients in the anti-platelet-only group (p = 0.22).

The RESPECT long-term study was a multicenter, randomized, open-label trial, with blinded adjudication of endpoint events [71]. Patients 18–60 years of age who had a PFO and had had a cryptogenic ischemic stroke were randomized to undergo closure of the PFO (PFO closure group) or to receive medical therapy alone (aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole; medical-therapy group). The primary efficacy endpoint was a composite of recurrent non-fatal ischemic stroke, fatal ischemic stroke, or early death after randomization. The study enrolled 980 patients (mean age 45.9 years). Patients were followed for a median of 5.9 years. In the ITT population, recurrent ischemic stroke occurred in 18 patients in the PFO closure group and in 28 patients in the medical-therapy group, resulting in rates of 0.58 events per 100 patient-years and 1.07 events per 100 patient-years, respectively (HR with PFO closure vs. medical therapy, 0.55; 95% CI 0.31–0.999; p = 0.046 by the log-rank test). Recurrent ischemic stroke of undetermined cause occurred in 10 patients in the PFO closure group and in 23 patients in the medical-therapy group (HR 0.38; 95% CI 0.18–0.79; p = 0.007).

Anti-Coagulation in Cerebral Ischemia of Non-Cardiac Origin

- Oral anti-coagulation is not superior to ASA and is not recommended.
- The benefit of anti-coagulation for patients with dissection of the vertebral or carotid arteries versus anti-platelet 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 anti-coagulation. The optimal treatment duration and specific coagulation disorders that warrant anti-coagulation are not clear.

The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) studied oral anti-coagulation 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 [72]. The study was terminated due
to a significantly increased bleeding risk with anti-coagulation. 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 [73]. This result was replicated in the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) study [74]. ESPRIT found a lower rate of ischaemic events with anti-coagulation relative risk [RR] 0.96, 95% CI 0.38–2.42; high-intensity anti-coagulation RR 1.02, 95% CI 0.49–2.13). The relative risk of major bleeding complications for low-intensity anti-coagulation was 1.27 (95% CI 0.79–2.03) and for medium-intensity anti-coagulation 1.19 (95% CI 0.59–2.41). High-intensity oral anti-coagulants with INR 3.0–4.5 resulted in a higher risk of major bleeding complications (RR 9.0; 95% CI 3.9–21) [75].

The Anti-Phospholipid Antibodies and Stroke Study (APASS) found no difference in stroke, MI, or vascular death in patients with anti-phospholipid antibodies (aPL) treated with warfarin (INR 1.4–2.8) compared to 325 mg ASA [76]. There was in addition no difference in event rates between patients positive or negative for aPL. The evidence for anti-coagulation 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 anti-coagulation, compared with anti-platelet drugs, for the long-term treatment of dissections was studied in the CADDIS trial [77]. The study recruited 250 with dissections of the carotid and vertebral arteries. Overall, four (2%) of 250 patients had stroke recurrence (all ipsilateral). Stroke or death occurred in three (2%) of 126 patients versus one (1%) of 124 (OR 0.335, 95% CI 0.006–4.233; p = 0.63). A Cochrane review of 26 observational studies in 327 patients found no difference between anti-coagulation and anti-platelet drugs for the endpoints death and severe disability [78]. Observational data indicate that NOACs might be as effective as warfarin with a better safety profile [79].

### 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 lower in patients with a stenosis between 50% and 70%, in high-degree stenosis (pseudo-occlusion), in women, and in cases when surgery is performed 12 weeks or later after the initial event.
- 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 [80–86]. 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 [86]. The risk reduction is even higher in stenosis >90%. In patients with 50–69% ICA stenosis the 5-year ARR for the end-point 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 [87].

Several studies randomized patients with significant ICA stenosis to carotid endarterectomy or balloon angioplasty with stenting. Surgeons and interventional
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neuroradiologists had to pass a quality control. SPACE randomized 1,200 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 [88]. 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 [89]. 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) [90]. Taken together the results of the two studies show a lower complication rate for endarterectomy. 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) [91]. 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 to be included in the study. Asymptomatic patients were eligible to participate if the degree of carotid stenosis was 60% or more on angiography, 70% or more on ultrasonography, or 80% 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 2,502 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 vs. 2.3% for endarterectomy, p = 0.01), whereas the risk of periprocedural myocardial infarction was higher in the endarterectomy group (1.1% for stenting vs. 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 years of age tended to do better with stenting, whereas those >70 years of age did better with endarterectomy. The Vertebral Artery Ischaemia Stenting Trial (VIST) study compared stenting versus best medical treatment in patients with symptomatic stenosis of the vertebral arteries. The study did not observe a difference, but was underpowered [92].

Symptomatic patients with significant stenosis of the internal carotid artery 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 [93].

Intracranial Stenosis

- Symptomatic patients with intracranial stenosis or occlusions should be treated with anti-platelet 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 anti-coagulation (INR 2.0–3.0) or ASA (1,300 mg/day). The study was terminated prematurely due to a higher rate of bleeding complications with warfarin [94]. 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 vertebrobasilar system, and female sex [95].

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 [96]. 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.

**Chapter Summary**

- **Anti-hypertensive therapy** reduces the risk of stroke. Most likely all anti-hypertensive drugs are effective in secondary stroke prevention. More important than the choice of a class of anti-hypertensives 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 anti-platelet 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 dual anti-platelet therapy (ASA plus clopidogrel) in patients with acute minor stroke or TIA and high risk of recurrence.
- Patients with a **cardiac source of embolism**, in particular atrial fibrillation, should be treated with oral anti-coagulation. Options for patients with AF include dose-adjusted warfarin (INR 2.0–3.0), apixaban, dabigatran, edoxaban, or rivaroxaban. Patients with contraindications or unwilling to use oral anti-coagulation should receive ASA 100–300 mg/day.
- In cerebral ischemia of **non-cardiac** origin oral anti-coagulation is not superior to ASA and is not recommended.
- Patent foramen ovale closure should be recommended as first-line treatment in patients with cryptogenic stroke below the age of 60 years and large PFOs.
- Symptomatic patients with significant **stenosis** of the **internal carotid artery** (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 anti-platelet therapy and high-dose statins (if deemed appropriate). In patients with recurrent events, angioplasty can be considered.

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