Primary and secondary prevention of cerebral ischemia

Joint Guidelines of the German Society of Neurology (DGN) and German Stroke Society (DSG)

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Bibliography
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Classification of level of evidence

↑↑ Efficacy and usefulness is well supported by multiple appropriate clinical studies (i.e. controlled randomized trials), either one or more metaanalyses or systematic reviews.
↑ Efficacy and usefulness is supported by at least one appropriate clinical study (i.e. controlled randomized trial).
↓↓ Lack of efficacy is well supported by one or more appropriate clinical studies (i.e. controlled randomized trial), either one or more metaanalyses or systematic reviews.
↔ No study results exist to prove any benefit or harm. This can be due lack of appropriate studies, or several studies with controversial results.

Strength of recommendation

A Strong recommendation derived from a high level of evidence or from lower evidence with high relevance for medical management
B Medium recommendation derived from a medium level of evidence or from low evidence with high relevance for medical management or from a high level evidence with limited relevance for medical management.
C Low recommendation derived from weaker evidence or from a higher level of evidence with limited relevance for medical management

What is new?

- The combination of oral anticoagulation and antiplatelet drugs in patients with atrial fibrillation and coronary heart disease should be avoided because it is associated with a higher rate of bleeding complications without reduction of vascular events (B)
- The combination of acetylsalicylic acid (ASA) and clopidogrel in patients with atrial fibrillation is less effective than oral anticoagulation with warfarin, but has an identical rate of severe bleeding complications (A)
- Oral anticoagulation after a TIA or an ischemic stroke is not more effective than the administration of ASA and thus cannot be recommended in general
- The combination of slow-release dipyridamole and ASA in secondary stroke prevention has the same effectiveness as clopidogrel monotherapy (A)
- The combination of 75 mg ASA and 75 mg clopidogrel is not more effective than treatment with only clopidogrel or acetylsalicylic acid but leads to a higher rate of bleeding complications (A)
- Angioplasty with or without stenting as a treatment for asymptomatic stenosis of the brain supplying arteries is not recommended (C)
- In patients with ischemic TIA / stroke (mod. Rankin < 3) without coronary heart disease and with an LDL-C-level between 100 and 190 mg / dl, 80 mg of atorvastatin daily is effective to reduce cardiovascular morbidity and recurrent stroke (A). However the reduction of LDL-C is probably more important than the use of a certain statin (C). It is therefore recommended to lower the LDL-C-levels with the use of a statin to < 100 mg / dl.
- Carotid endarterectomy is the treatment of choice in high-grade symptomatic carotid stenosis (A). Carotid angioplasty and stenting is not a routine procedure yet. In comparison to surgical therapy, angioplasty and stenting have a slightly higher short-term risk relating to periprocedural complications (30 days). Protection devices do not reduce the complication rate (B). With both methods there is a high variation in complication rates. Therefore,

the individual complication rate of the surgeon or interventionalist must contribute to the decision making process. In patients over 65–68 years of age the surgical treatment has a lower complication rate than stenting. The long-term results (2–4 years) regarding stroke are the same for both treatments. The rate of restenoses is higher after stenting.

- Before, during and after carotid surgery prophylaxis with ASA should be continued (B).
- Treatment of hyperhomocysteinemia with vitamin B6, B12 and folic acid for secondary stroke prevention is ineffective (A).
- The early secondary prophylaxis of an ischemic insult with telmisartan in addition to a common antihypertensive therapy does not show superiority to placebo (A).

The most important recommendations at a glance

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Primary prevention – Risk factors

- A „healthy lifestyle“ including at least 30 minutes of sporting activity 3 times a week and diet that is rich in fruits and vegetables,
  „Mediterranean cooking“, respectively, is recommended for primary stroke prevention (A). Cardiovascular risk factors (blood pressure, blood glucose, and lipid disorders) should be checked routinely and treated when abnormal (B)
- Patients with arterial hypertension (RR systolic > 140 mm Hg, diastolic > 90 mm Hg, diabetics: RR systolic > 130 mm Hg, diastolic > 80 mm Hg) should be treated with diets (DASH-diet, low-salt diet), aerobic exercise and / or antihypertensive drugs (A). The preventive effect of antihypertensive medication increases with the amount of blood pressure reduction (A). The individual antihypertensive drugs differ only slightly in their stroke preventive effect. Alpha-blockers are less effective that other agents.
- Smokers should cease nicotine consumption. There is proof for the effectiveness of pharmacologic (nicotine patch, nicotine chewing gum, anti-craving-therapy with tricyclic antidepressants, buproprion or varenicline) or non-pharmacologic therapy (behavioural therapy, group therapy) (B).
- Patients with coronary heart disease or a history of myocardial infarction and LDL-cholesterol level of > 100 mg / dl should be treated with a statin (A). Persons without coronary heart disease should be treated with a statin when they have at least one vascular risk factor and LDL-C-levels > 190 mg / dl, if they are at medium risk and have LDL-cholesterol > 160 mg / dl or if they have LDL-C > 100 mg / dl and several vascular risk factors. Most evidence is available for simvastatin, pravastatin and atorvastatin.
- Diabetics should be treated with diet, regular exercise, antidiabetics and if needed insulin. It should be aimed for normoglycemic blood sugar levels. In diabetic patients the treatment of hypertension with ACE-inhibitors or sartans and statins is especially important for stroke prevention.

Primary prevention – Atrial fibrillation

- Patients with persistent or paroxysmal atrial fibrillation and accompanying vascular risk factors (arterial hypertension, coronary heart disease, cardiac failure, age > 75 years) should be anticoagulated orally with an INR of 2.0–3.0 (A). Patients > 75 years should have an INR of approximately 2.0. In the rare event of a so called lone atrial fibrillation, which means atrial fibrillation, age < 65 years and no vascular risk factors, neither anticoagulation nor use of antiplatelet drugs is necessary. In patients without risk factors older than 65 yeas and atrial fibrillation acetylsalicylic acid (ASA; 100–300 mg daily) is recommended (B). ASA is also recommended for use in patients with contraindications for anticoagulation like severe cerebral microangiopathy, dementia and increased risk of falls.
- The combination of oral anticoagulation and antiplatelet drugs in patients with atrial fibrillation and stable coronary heart disease should be avoided as this leads to a higher risk of bleeding complications without a reduction of vascular events (B).

Primary prevention – antiplatelet drugs

- Acetylsalicylic acid (ASA) is not effective in primary prevention of stroke in male patients (A).
- In female patients > 45 years and with vascular risk factors, administration of ASA reduces the risk of stroke but not of myocardial infarction (B). The risk reduction is low and benefit and risk (bleedings, gastrointestinal intolerance) must be weighed against each other thoroughly.

Primary prevention – high-grade stenosis of the internal carotid artery

- The operation of an asymptomatic stenosis of the internal carotid artery of > 60 % lumen reduction according to Doppler- or duplexsonographic criteria reduces the risk for stroke significantly. However, this is only true if the combined morbidity and mortality rate of the procedure within 30 days is below 3 % (A). Life expectancy should be greater than 5 years. Male patients profit more of the procedure than women.
- Angioplasty with or without stenting as treatment for asymptomatic stenosis of the brain supplying arteries is not recommended (C).

Secondary prevention of stroke – risk factors

- Antihypertensive therapy reduces the risk for stroke (A). As this is true for patients with arterial hypertension as well as without, this recommendation should be considered in all patients after a TIA or stroke (B).
- Which antihypertensive class is the most effective in secondary prevention of stroke is still a subject for discussion. The combination of perindopril and indapamide is significantly more effective than placebo (A) and eprosartan is significantly more effective than nitrendipine (A). In patients after stroke, ramipril reduces vascular endpoints (B).
- Early secondary prevention of ischemic stroke with telmisartan in addition to a common antihypertensive therapy shows no superiority to placebo (A).
- Modification of certain life habits can reduce high blood pressure levels and should complement medical treatment (C).
- In patients with focal cerebral ischemia and coronary heart disease statins should be used, regardless of initial LDL-cholesterol levels (A). The target value should be between 70 and 100 mg / dl. In patients with ischemic TIA / stroke (mod. Rankin < 3) without coronary heart disease with LDL-C-levels between 100 and 190 mg / dl, 80 mg of atorvastatin is effective to reduce the risk of recurrent stroke and cardiovascular morbidity (A). However, the reduction of LDL-cholesterol is more important than the use of a certain statin (C). It is therefore recommended to reduce the LDL-C-level below 100 mg / dl

with a statin. The benefit of this treatment is highest if the LDL-C-level is reduced to at least 50 % of the initial value. In patients with a haemorrhagic TIA / stroke prophylaxis with atorvastatin should only be used as an exception (for instance in cases of cardiovascular disease) (B).

- The treatment of a hyperhomocysteinemia with vitamin B6, B12 and folic acid is not effective in secondary stroke prevention (A).
- Hormone substitution after the menopause is not effective in secondary prophylaxis of stroke (B).

Secondary prophylaxis – antiplatelet drugs

- In patients with a focal ischemia, antiplatelet drugs are effective as secondary prevention (A). This is true for acetylsalicylic acid (ASA; 50–150 mg) (A), the combination of ASA (2 × 25 mg) and slow-release dipyridamole (2 × 200 mg) (A) and clopidogrel (75 mg) (B).
- In patients after TIA and ischemic stroke with a low risk of recurrent stroke (< 4 % per year) the administration of 100 mg of ASA daily is recommended (A).
- In patients with a high risk of recurrent stroke (≥ 4 % per year) a fixed combination of 25 mg ASA and 200 mg slow-release dipyridamole bid or clopidogrel 75 mg are recommended.
- In patients with contraindications or intolerance to ASA, clopidogrel 75 mg is recommended.
- The combination of slow-release dipyridamole and ASA in secondary prophylaxis of stroke is as effective as monotherapy with clopidogrel (A).
- ASA in dosages of > 150 mg leads to a higher risk of bleeding complications (B).
- The combination of 75 mg ASA and 75 mg clopidogrel is not more effective than monotherapy with either clopidogrel or ASA but leads to more bleeding complications (A).
- In patients who develop a gastric or duodenal ulcer during secondary prevention with ASA, it is recommended to continue the ASA-therapy in combination with a proton pump inhibitor after an adequate healing period (B).
- In case of recurrent stroke or TIA during the intake of ASA, the pathophysiology and risk for another recurrent stroke should be evaluated again (C). If a cardiac source of embolism is found, oral anticoagulation is started. If the risk of recurrent stroke has not changed, the prophylaxis with ASA can be continued (C). If the risk of recurrent stroke has increased the prophylaxis is conversed to either a combination of ASA with slow-release dipyridamole or clopidogrel (C).
- GP-IIb / IIIa-antagonists should not be used for secondary stroke prevention (A). They are not more effective as acetylsalicylic acid, but cause a higher risk for bleeding complications.

Secondary prophylaxis – atrial fibrillation

- In patients with a cardiac source of embolism, in particular with atrial fibrillation, an oral anticoagulation with INR-levels from 2.0–3.0 is recommended (A).
- After TIA or minor ischemic stroke and atrial fibrillation oral anticoagulation can be initiated within 3–5 days (C).
- In patients with mechanical heart valves anticoagulation is continued with INR-levels between 2.5 and 3.5 (C).
- In patients with biological valves and cerebral ischemia a temporary anticoagulation for 3 months is recommended (C).

Secondary prophylaxis – non-cardiac source of embolism

- Oral anticoagulation after TIA or ischemic stroke is not more effective than administration of ASA and therefore cannot be recommended (A).
- In cases of dissection of the extracranial brain supplying arteries, a temporary anticoagulation for 6 months should be initiated (C). However, a superiority compared to antiplatelet drugs is not proven.
- In young patients with protein-C, -S or antithrombin-deficit as well as homozygous factor-V-(Leiden)-mutation and with otherwise cryptogenic cause of stroke a permanent anticoagulation is recommended (C).

Secondary prophylaxis – patent foramen ovale (PFO)

- In patients with a PFO alone, regardless of size, and a first cerebral ischemic incident a prophylaxis with acetylsalicylic acid (ASA; 100 mg) is recommended (B).
- Does a recurrent stroke occur during the therapy with ASA or is a PFO combined with an atrial septum aneurysm, oral anticoagulation with an INR of 2.0–3.0 for 2 years is recommended (C).
- In case of another recurrent stroke or contraindications for oral anticoagulation, interventional closure of the PFO can be considered (C).

Secondary prophylaxis – high-grade stenosis of the internal carotid artery

- To diagnose a stenosis of the carotid artery, ultrasound, MRI- or CT-angiography are sufficient (A). DSA is usually not necessary (B).
- In high-grade symptomatic carotid artery stenosis, endarterectomy (CEA) should be performed (A). The benefit of the operation increases with the degree of stenosis between 70 and 95 %. In stenosis between 50 and 70 %, in women and if the operation is performed later than 12 weeks after the index incident there is no more benefit of CEA (A).
- The benefit of the operation no longer exists if the complication rate is higher than 6 %.
- The time between the incident and the operation should be covered with administration of antiplatelet drugs (B). ASA should be continued before, during and after the operation (B). Clopidogrel should be substituted by ASA at least 5 days prior to the operation (C).
- Carotid angioplasty and stenting (CAS) is no routine procedure yet. In comparison to the surgical treatment of symptomatic carotid stenosis it has a slightly higher short-term risk (30 days) concerning the periprocedural risk (A). The use of protection devices does not lower the complication rate (B). The complication rates for CAS as well as CEA have a high variation. Therefore, the complication rate of the treating interventionalist has to be included in the therapeutical decision. The long-term results (2–4 years) regarding stroke are comparable for both methods. The restenosis rate is higher in stenting.
- At present, carotid endarterectomy still is the first choice treatment (A). Stenting (with angioplasty if applicable) can be considered in patients with restenosis after CEA, high-grade stenosis after radio therapy or a very distal stenosis where an operation is technically difficult (C).
- Before, during and after stenting a prophylaxis with clopidogrel (75 mg) plus ASA (100 mg) is given for 1–3 months.

Intracranial stenosis

- In patients with high-grade intracranial stenosis or occlusion, a secondary prophylaxis with antiplatelet drugs is recommended (B). Due to the poor tolerance of the evidence based dosage of 1300 mg ASA, we recommend a prophylaxis with 100–300 mg acetylsalicylic acid (ASA) (C).
- In patients with recurrent ischemic events a stent implantation in a centre with adequate neuroradiological experience can be considered (C). This is followed by a treatment with 75 mg of clopidogrel and 100 mg of ASA for 1–3 months (C).

Primary Prevention

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Goals

The goal of primary prevention is to avoid cerebral ischemia or transient ischemic attacks (TIAs) in patients with no previous cerebrovascular diseases. Patients can be classified into four different sub-groups:

- completely healthy persons
- persons with no significant disease but with vascular risk factors
- persons with asymptomatic stenosis or occlusion of the arteries supplying the brain
- patients with vascular disease in other regions (MI, coronary heart disease, peripheral artery disease [PAD])

It is assumed that, in principle, risk is the lowest for completely healthy persons and increases in the order as listed above, with patients with vascular disease in other regions carrying the highest risk. This assumption should influence the strategies of prevention. Unfortunately, studies to date have not compared the effect of primary stroke prevention in these patient collectives.

Epidemiology

Depending on their geographical allocation, studies have reported 100–700 strokes occurring per 100,000 people per year. The highest incidences are found today in the east European countries, while the rates in west European countries, Scandinavia and North America are relatively low (Khaw 1996, Bejot et al. 2007).

Examinations

Necessary

- Recording of vascular risk factors (blood pressure, blood sugar, cholesterol incl. LDL and HDL)
- ECG
- Neurological and medical examination

Additionally required in individual cases

- Ultrasound of the extra- and intracranial arteries
- Echocardiography
- CT to exclude clinically silent ischemia or subcortical vascular encephalopathy in long term arterial hypertension.

Therapy

Recommended Therapy

- For primary stroke prevention a „healthy lifestyle“ is recommended, with at least 30 minutes of exercise 3 times a week and a diet rich in fruits and vegetables or a Mediterranean diet (A). Cardiovascular risk factors should be checked at regular intervals (blood pressure, blood sugar, fat metabolism disorders) and pathological findings corrected (B).
- Overweight patients should keep a weight reducing diet and exercise regularly.
- Patients with arterial hypertension (systolic RR > 140 mm Hg, diastolic RR > 90 mm Hg; for diabetics: systolic RR > 130 mm Hg, diastolic RR > 85 mm Hg) should be treated with a diet (DASH-Diet, low-salt diet), endurance sports and / or antihypertensive drugs (A). The preventive effect of antihypertensive medication increases as blood pressure is reduced (A). The various agents differ little in their stroke-preventive effect (A). Alpha blockers are less effective than other antihypertensive drugs (B). It is mainly the level of blood pressure reduction that determines preventive benefit.
- Smokers should stop their nicotine consumption. Pharmacologic (nicotine patches, nicotine chewing gum, anti-craving therapy with tricyclic antidepressants, buproprion or vareniclin) or non-pharmacologic aids (behavioural therapy, group therapy) have shown their effectiveness (B).
- Patients with coronary heart disease or a history of myocardial infarction and a LDL-cholesterol level of > 100 mg / dl should be treated with a statin (A). Persons without coronary heart disease should be treated with a statin when they have one vascular risk factor at the most and LDL-C-levels > 190 mg / dl, at medium risk and LDL-cholesterol > 160 mg / dl or > 100 mg / dl combined with several vascular risk factors. The statins with the most supportive evidence available are simvastatin, pravastatin and atorvastatin.
- Diabetics should be treated with diet, regular exercise, antidiabetics and if needed insulin. The goal should be normoglycemic blood sugar levels. Treatment of hypertension with ACE-inhibitors or sartans and statins is especially important for stroke prevention in diabetic patients.
- Patients with persistent or paroxysmal atrial fibrillation and accompanying vascular risk factors (arterial hypertension, coronary heart disease, cardiac insufficiency, age > 75 years) should be administered oral anticoagulates with an INR of 2.0–3.0 (A). Patients > 75 years should have an INR of approximately 2.0. In the rare event of a so-called lone atrial fibrillation, i. e. atrial fibrillation, age < 65 years and no vascular risk factors, neither anticoagulation nor inhibition of thrombocyte function is necessary. In patients older than 65 years without risk factors but with atrial fibrillation, acetylsalicylic acid (100–300 mg daily) is recommended (B). ASA is also recommended for use in patients with contraindications for anticoagulation such as severe cerebral microangiopathy, apparent dementia or increased risk of falling.
- The combination of ASA and clopidogrel in atrial fibrillation is less effective than oral anticoagulation with warfarin but shows the same rate of severe bleeding complications (A).
- Oral anticoagulation as a means of stroke prevention following bioprosthetic heart-valve replacement is not necessary for longer than 3 months post-operation.
- An asymptomatic patent foramen ovale (PFO) with or without atrial septum aneurysm does not require special treatment (A).
- Acetylsalicylic acid (ASA) is not effective in primary stroke prevention for male patients (A).
- In female patients over 45 years and with vascular risk factors, administration of ASA reduces the incident of stroke but not of myocardial infarction (B). The risk reduction is low and its benefits must be weighed against risks associated with it (bleedings, gastrointestinal intolerance).

- The operation of an asymptomatic stenosis of the internal carotid artery with >60% stenosis according to Doppler- or duplexsonographical criteria significantly reduces the risk of stroke. This applies, however, only if the combined morbidity and mortality of the procedure is below 3% within 30 days (A). Life expectancy should be greater than 5 years. Male patients profit more from this procedure than women.
- Angioplasty with or without stenting is not recommended as treatment for asymptomatic stenosis of arteries supplying the brain (C).

Not recommended treatment

- Alcohol should not be imbibed as a means of primary prophylaxis (C).
- Hormone substitution therapy after menopause increases the risk for stroke (A).
- Vitamins, especially vitamin E, A and C are ineffective in primary prophylaxis (A).
- Reducing an elevated homocysteine count with folic acid and B-vitamins does not lower the risk of stroke (B).
- Garlic products and so called nootropics are ineffective in the prophylaxis of stroke (B).
- Polypragmatic therapies combining vitamins, ASA, statins, folic acid, trace elements are not recommended (B). Antioxidants (vitamin E and C) can have a negative influence on the effectiveness of statins.
- Antiplatelet drugs such as clopidogrel, ticlopidin or the combination of ASA plus dipyridamole should not be used in primary prophylaxis (B).
- ASA and oral anticoagulants should not be used in combination. The combination of 325 mg ASA daily and anticoagulation with an INR of 1.25–1.5 does not benefit patients with atrial fibrillation (B) but does increase the risk of bleedings.
- The operation of an asymptomatic carotid stenosis by surgeons with a complication rate >3% is not indicated (B).
- The anticoagulation of patients with mitral valve prolapse syndrome is not indicated (A).

Identification and treatment of vascular risk factors

Arterial hypertension

The treatment of arterial hypertension is very important for primary stroke prevention. According to numerous studies, the treatment of arterial hypertension leads to a drastic reduction of the risk for ischemic as well as hemorrhagic strokes. Even a moderate and easily achievable reduction of systolic and diastolic blood pressure by 5–6 mm Hg and 2–3 mm Hg, respectively, leads to a relative risk reduction of approximately 40% (Collins et al. 1990). The absolute RRR is approximately 0.5% per year, which means that 200 patients with arterial hypertension have to be treated to prevent one stroke. This effect is observed in all age groups and types of hypertension, including patients older than 80 years and those with isolated systolic hypertension (Staessen et al. 2000, Staessen et al. 2001). The best time to start an antihypertensive treatment depends on accompanying risk factors determining the global risk, on any other organ dysfunctions or on accompanying diseases according to a recommendation of the WHO and the German Hypertension Society. **Table 1** gives an overview of the vascular risk factors on which treatment recommendations are based.

The target level after blood pressure reduction will depend on the risk profile and is about 10 mm Hg lower in diabetics. The minimum goal is an upper limit of <140 mm Hg for systolic and <90 mm Hg for diastolic blood pressure. In principle, the preventive effect increases in a linear manner with the reduction of blood pressure. If tolerated by the patient, a reduction to the optimal range of <120/80 mm Hg is recommended.

Before pharmacologic therapy is begun, the importance of non-pharmacologic measures should be made clear to the patient. These measures should always be included in the therapy and are especially effective with young patients. For antihypertensive treatment there are no proven differences between the following five substance categories: Angiotensin-converting-enzyme- (ACE-) inhibitors, angiotensin receptor (AT) blockers, betablockers, calcium antagonists and diuretics (Droste et al. 2003, International Society of Hypertension Writing Group 2003).

A comparison between conventional antihypertensives (atenolol, metoprolol, pindolol, hydrochlorothiacide plus amilorid) and newer agents (enalapril, lisinopril, felodipin, isradipin) showed no significant differences in the rate of stroke in elderly patients (Hansson et al. 1999), so that each of these can be seen as treatment of first choice. All in all, the level of blood pressure reduction achieved determines how useful the therapy has been. Differences between certain monotherapies were based more on blood pressure differences than on substance-specific properties. In a recently published meta-analysis the betablocker atenolol was inferior to other antihypertensives in primary prevention in patients without coronary heart disease (Lindholm et al. 2005). This trend was also demonstrated by a slight superiority of AT1-blockers and calcium antagonists in the prevention of cerebrovascular events in comparison to other substance classes (Staessen et al. 2001). Lorsatan is more effective than atenolol, but showed similar effectiveness in lowering the blood pressure (Dahlof et al. 2002, Lindholm et al. 2002). Any convincing differences in total mortality or cardiovascular events have yet to be demonstrated. In patients with arterial hypertension lorsartan offers special protection from stroke in patients with left-ventricular hypertrophy or newly developed atrial fibrillation. In contrast to this, the preventive effectiveness of alpha-receptor blockers is significantly lower, so that this substance class cannot be seen as a first choice therapy option (The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2000). According to the current recommendations, a primary

Table 1 Factors that influence the risk profile of patients with arterial hypertension. For risk assessment according to WHO the categories I, II and III are used.

Category	Description
I. Vascular risk factors for assessment	Positive family history for vascular diseases (only relatives of 1st order) Men >55 years of age, Women >65 years of age Smoking Hyperlipidemia Diabetes mellitus
II. Organ damage	Left ventricular hypertrophy Nephropathy: microalbuminuria, proteinuria or slight creatinine elevation Hypertensive retinopathy Proof of arteriosclerotic plaques in large arteries such as the carotid arteries
III. Resulting and accompanying disease	Ischemic brain insult CHD, MI, ACVB operation PAD

CHD = coronary heart disease, PAD = peripheral artery disease, ACVB = aorto-coronary venous bypass.

combination therapy (for example ACE-inhibitor or betablocker plus diuretic) is equivalent to a multi-step therapy (monotherapy, different monotherapy, combination therapy). More than two thirds of all patients need an antihypertensive combination therapy to achieve their goal. The ASCOT study gives evidence for this. In this study, the combination of an ACE-inhibitor and a calcium antagonist was superior in stroke reduction than atenolol and hydrochlorothiacide, but the reduction of blood pressure was also greater (Dahlof et al. 2005).

As shown in the DASH study, dietary measures (low-salt food and a diet that includes large volumes of fruits, vegetables, low fat milk, poultry, fish and cereal) can be effective in lowering blood pressure. In the course of a special DASH diet including salt reduction, the mean RR was lowered by approximately 11 mm Hg. A corresponding preventive effect on cardiovascular and cerebrovascular events was not proven (albeit the number of cases was not high enough).

Smoking

Smoking increases the risk of stroke by 1.8–3.7 times without a lower threshold (Shinton and Beevers 1989, Kawachi et al. 1993, Wannamethee et al. 1995, Goldstein et al. 2001, Iso et al. 2005). This is also true for passive smoking (Heuschmann et al. 2007). It always pays to quit smoking, as stroke risk decreases to the level of non smokers within 5 years (Kawachi et al. 1993, Wannamethee et al. 1995, Keilh et al. 2006). Randomised studies on the effect of giving up smoking are not yet available. Epidemiological studies show that the elevated risk for strokes can be clearly reduced by nicotine abstinence.

Remarkably, after 12 months of abstinence a reduction of the vascular risk to one half can already be observed; after another 5 years the vascular risk profile is only slightly above that of a non-smoker (Wilson et al. 1985, Kawachi et al. 1993, Wilson et al. 1997, Keil et al. 2006). A newer case-control-study of Hong Kong-Chinese older than 65 years showed that tobacco abstinence is still beneficial at higher ages („Quitting is beneficial") (Lam et al. 2007).

Surveys showed that approximately 70% of all smokers would like to quit smoking and over 40% have already tried at least once. Only 10% (that means an absolute 3–4%) successfully withstand the withdrawal syndrome by force of willpower alone. Many try to reduce withdrawal symptoms by means of nicotine preparations in the form of chewing gum, nicotine patches, nasal sprays, inhalation aerosols and cough drops. A meta-analysis analysis of the Cochrane Library (Hughes et al. 2007) showed an odds-ratio of 1.5–2.7 for successful nicotine abstinence using pharmaceutical nicotine preparations compared to placebo during an observation period of 6 months and more.

The antidepressant buproprion – a pharmacotherapeutic – is more effective in supporting nicotine abstinence than placebo and nicotine patches. The odds-ratio compared to placebo was 1.43–2.13 (Hughes et al. 2007). Addictive behaviour towards nicotine is mediated by a subtype of the nicotinic acetylcholine receptor in the ventral tegmentum. As a partial agonist, vareniclin reverses withdrawal symptoms, and as a partial antagonistic it suppresses intensification of the addiction. In randomised double blind trials, vareniclin was superior to placebo as well as to bupropion and was tolerated well (Gonzales et al. 2006, Jorenby et al. 2006). In 3-armed trials, the success rate of long-term tobacco abstinence with vareniclin was almost 44% compared to 17.6% in the placebo and almost 30% in the buproprion group. The abstinence rates after one year were 23%, 10.3% and 14.6%, respectively. Nausea and insomnia were the most common side effects of vareniclin, with an incidence of 29% and 14%, respectively.

Immediate and total cessation of nicotine consumption can be achieved better with **psychotherapeutic-psychological help** than without (B). Limited effectiveness for tobacco abstinence has been shown for 1. professional counsel, 2. social support or 3. „**comprehensive tobacco control strategies**" of whole nations. A short informational conversation with a physician, including the advice to stop smoking, is statistically only successful in 5% of all cases, in combination with detailed information material and counselling this rate can be increased to 10%. A nicotine substitution therapy doubles the rate and should be considered when the patient shows sufficient motivation and has a history of unsuccessful attempts at abstinence.

Nicotine abstinence is a cheap and effective instrument for primary prevention and leads to a significant risk reduction (↑↑) (A). Given sufficient abstinence motivation either a nicotine substitution therapy should be started, for instance with nicotine patches or chewing gum or an anti-craving therapy with tricyclic antidepressants (↑) (B) or more effectively with buproprion (↑↑) (A) or vareniclin (↑↑) (A).

Hypercholesterolemia

Field studies could not show a clear connection between cholesterol levels and stroke incidence. This is probably due to the fact that they included hemorrhagic strokes (Iso et al. 1989, Lewington et al. 2007). Newer studies consistently show that the risk for an ischemic stroke increases with higher cholesterol levels in both men and women (especially >240–270 mg/dl) (Leppala et al. 1999). However, the connection between stroke risk and LDL-cholesterol remains unclear (Shahar et al. 2003). Low HDL-cholesterol in men, but not clearly in women, is associated with a higher risk for ischemic stroke (Wannamethee et al. 2000).

Based on numerous large randomised studies (for instance CARE, 4S, LIPID, HPS, see also Paciaroni et al. 2007) HMG-CoA reductase inhibitors (statins) are approved for the protection against ischemic stroke in patients with a manifest CHD or history of myocardial infarction. The relative risk reduction (RRR) due to use of statins is 30–40% for myocardial infarction and 21% for stroke (Amarenco et al. 2004). In CARDS 2,838 patients were treated with 10 mg of either atorvastatin or placebo. The NNT for vascular events was 27 for 4 years, during which 39 strokes occurred in the placebo-group and 21 in the atorvastatin-group (48% RRR) (Colhoun et al. 2004). In the ASCOT trial, patients with arterial hypertension and other risk factors were treated with either 10 mg atorvastatin or placebo. During this time the absolute risk reduction (ARR) for vascular events was 1.9% for 3.3 years; the NNT was 53. An RRR for stroke of 27% was shown, although the absolute numbers were low (89/atorvastatin; 121/placebo; Sever et al. 2003). In the PROSPER trial, high risk patients older than 79 years of age were observed. Here, no improvement in the stroke rate could be found for therapy with statins (Shepherd et al. 2002). The MIRACL trial showed a superiority of 80 mg atorvastatin versus placebo in the early secondary prevention after an acute coronary syndrome. In a low absolute risk of 1.6 vs. 0.8% over a period of 16 weeks, ischemic brain infarctions were reduced by 50% (Waters et al. 2002).

Newer studies tried to show whether an aggressive statin therapy is more effective than a moderate therapy in high risk patients. In the PROVE-IT study a superiority of 80 mg atorvastatin over pravastatin was demonstrated in patients with acute coronary syndrome; the ARR for atorvastatin vs. pravastatin was 3.9%

over a period of 2 years, the NNT 26 for 2 years (Cannon et al. 2004). In the A-to-Z trial, the early use of 40/80 mg of simvastatin in patients with an acute coronary syndrome did not prove to be more effective regarding the primary endpoint than the delayed administration of 20 mg of simvastatin (de Lemos et al. 2004). In patients with a stable coronary heart disease the TNT-trial showed an advantage of 80 vs. 10 mg of atorvastatin (25% RRR for stroke, in absolute terms 3.1% vs. 2.3%) (LaRosa et al. 2005). In conclusion, these studies show that high risk patients benefit from an aggressive therapy and an LDL-C-level < 70 mg/dl.

The guidelines of the NCEP ATP III define 3 distinct risk groups:

1. no (or max. 1) risk factor
2. multiple (> 2) risk factors
3. apparent CHD or CHD-equivalent

Their recommendations depend on the LDL-cholesterol levels (LDL-C) and the risk profile:

- In patients with no apparent CHD and 0–1 risk factors, a statin can be given at LDL-C-levels > 160 mg/dl and should be given at LDL-C-levels > 190 mg/dl (target value LDL-C < 160 mg/dl). Non-medical measures include diet, weight reduction and sports activities.
- In patients with ≥ 2 vascular risk factors (10-year-CHD-risk < 20%) a statin can be given at LDL-C-levels > 130 mg/dl and should be given at LDL-C-levels > 160 mg/dl (target value LDL-C < 130 mg/dl).
- In patients with a CHD, a history of myocardial infarction or an equivalent risk (10-year-CHD-risk > 20%, for example in diabetes (Colhoun et al. 2004) a statin should be given at LDL-C-levels > 100 mg/dl and in high risk patients at LDL-C-levels > 70 mg/dl (target value < 100 mg/dl, in high risk patients < 70 mg/dl).

Statins have additional cholesterol-independent (pleiotropic) effects (anti-inflammatory, immunomodulatory, plaque-stabilizing, vasodilatatory, blood pressure lowering effects). Most pleiotropic effects are caused by HMG-CoA-reductase inhibition and are dose-dependent. Accordingly, their behaviour is analogous to the reduction in LDL-C-level.

Diabetes Mellitus

Diabetes mellitus is a relevant and independent risk factor for strokes. Most studies concerning primary prevention showed no significant stroke risk reduction for stroke or any other macrovascular complications after a strict antidiabetic therapy (Turner et al. 1999). In the UKPDS trial a 25% risk reduction for microvascular secondary diseases was found in the intensified therapy group in comparison to the conventional treatment group (UK Prospective Diabetes Study [UKPDS] Group 1998, Stratton et al. 2000). In the STENO-2-study intensified antidiabetic treatment compared to conventional guideline-oriented therapy led to a 50% reduction of cardiovascular complications (Gaede et al. 2003). However, in the ACCORD study a higher mortality was found in patients in whom the blood sugar level was lowered very aggressively. Also by lowering the antihypertensive target range alone, independent of the antidiabetic therapy, the stroke risk can be reduced by almost one half. Blood pressure levels of < 130/85 mm Hg are commonly recommended. In diabetics this should be achieved by influencing the renin-angiotensin-aldosterone-system (RAAS), so that ACE-inhibitors and AT1-blockers are the first choice. A meta-analysis of the cholesterol Trialists' Collaboration concludes that a statin therapy leads to a relative risk reduction for stroke of 21% for every mmol/l by which LDL-C is lowered (Cholesterol Treatment Trialists' [CTT] Collaborators 2008).

Overweight

Overweight and obesity are defined as body mass index (BMI = weight/height^2) between 25 and 30 kg/m^2 and > 30 kg/m^2, respectively. Abdominal adiposity can be assessed by the proportion of hip to waistline or the waist circumference (> 102 cm in men, > 88 in women). Overweight is a modifiable vascular risk factor, especially for coronary heart disease. Overweight increases the risk for arterial hypertension, diabetes mellitus and dyslipidemia. The stroke incidence of overweight persons is elevated. The effect, which shows a dose-dependency, is still observed after control of other vascular risk factors in multivariate analysis (Kurth et al. 2002).

A reduction of obesity has a positive effect on the associated risk factors (arterial hypertension, diabetes, and hypercholesterolemia). The anti-hypertensive effect was documented in a meta-analysis of 25 studies: weight loss of 5 kg lowers systolic and diastolic blood pressure by an average of 4.4 and 3.6 mm Hg, respectively (Neter et al. 2003). Even though a positive effect on stroke risk seems plausible, the protective effect of weight loss on stroke-incidence and mortality has not yet been sufficiently investigated. There are no data available from randomised studies (↔) (Curioni et al. 2006). Rimonabant reduces the weight of obese persons by 4–6 kg over a period of 6 months (Pi-Sunyer et al. 2006, Scheen et al. 2006). Whether this has an effect on vascular endpoints is still under investigation. Rimonabant should not be used in patients with depression and anxiety disorders (Christensen et al. 2007).

Lack of physical activity

Sports activities have, like weight loss in obesity, mainly indirect effects on stroke risk, because they modify other risk factors such as arterial hypertension, hypercholesterolemia, and diabetes mellitus. Additionally, a positive effect on blood rheology and platelet reactivity has been described. A gender-independent risk reduction by 40–60% due to regular physical activity has been found in several studies (Abbott et al. 1994, Kiely et al. 1994, Lee et al. 1999, Lee et al. 2003). To have a protective effect, physical activity had to lead to either an increase of the heart rate or increased sweat production. The risk of ischemic strokes and also for cerebral bleeding was reduced, which is mainly ascribed to the reduction of blood pressure. It is noteworthy that there is no apparent linear dose-effect relationship but instead a constant class effect. The risk reduction in the Physicians Health Study and the Framingham Study was comparable for sports activities once a week and light activities in multiple trainings per week or heavy activities (Kiely et al. 1994).

Hyperhomocysteinemia

It has been shown in numerous studies that by modifying the diet with increasing supplements of vitamin B6, B12 and folic acid or direct intake of these vitamins, the serum homocysteine levels could be lowered. A large scaled investigation showed that by enrichment of muesli products with folic acid, the serum folic acid level was increased by 60% while the homocysteine level was lowered by 10–15%. However, there is still no proof that the cerebral or vascular risk can be lowered by reduction of homocysteine levels (The Heart Outcomes Prevention Evaluation [HOPE] 2 Investigators 2006).

Other risk factors

Female sex hormones, used either for contraception or postmenopausal hormone replacement therapy (HRT) increase the risk for vascular events including stroke. This is also true for women with an oestrogen substitution after hysterectomy. The HRT has no protective effect on cardiovascular morbidity or mortality (↓↓) (Burry 2002, Grady et al. 2002, Anderson et al. 2004).

Migraine is a risk factor for stroke (Merikangas et al. 1997, Diener et al. 2004b). The risk is increased only for women who suffer from migraine with aura and arterial hypertension and who smoke and take the pill. Studies which investigate the effect of migraine prophylaxis are not available. However, female risk patients should be treated for their risk factors.

There are no data available regarding primary prophylaxis of stroke for the following, still unconfirmed risk factors: sleep-apnoea-syndrome, chronic infection, chronic inflammation and depression.

Primary prevention with antiplatelet drugs

Two large studies investigated the primary prophylactic intake of ASA (Peto et al. 1988, The Steering Committee of the Physicians' Health Study Research Group 1988). A significant risk reduction could be shown for heart attacks but not for cerebral infarctions. Intracranial bleedings were more frequent under ASA. The Nurses Health Study could not show an advantage of ASA in stroke prevention in women (Iso et al. 1999). However, the Womens Health Study showed a benefit of acetylsalicylic acid in primary stroke prevention in women >45 years (RRR = 17%) (Ridker et al. 2005). A large meta-analysis including more than 250,000 individuals in 5 trials (Hart et al. 2000b) taking 75–650 mg ASA / day could not demonstrate an advantage for ASA because the annual stroke risk was very low (0.3%) and the relative risk for intracerebral bleedings was increased by 8%. In the „Primary Prevention Project"-study, diabetics did not benefit from a prophylactic intake of ASA (Collaborative Group of the Primary Prevention Project [PPP] 2001).

Primary Prevention in Atrial Fibrillation (AF)

In a meta-analysis of 5 randomised studies for primary prevention in AF, a RRR of 70% could be reached by oral anticoagulation with a target INR of 2.0–3.0 in comparison to placebo treatment (↑↑) (Hart et al. 1999). The absolute RR due to effective anticoagulation is approximately 3% per year, which corresponds to a NNT of 33. A less aggressive anticoagulation with a target INR of 1.5–1.9, so called „warfarin light", has almost no benefit. Anticoagulation with a target INR of 3.0–3.9 led to reduction of any stroke by only 40% due to an increased rate of cerebral haemorrhage. An exponential increase for the risk of cerebral bleedings was observed with an INR of >4.5. Thereafter, every INR-increase of 0.5 points caused a doubling in risk for cerebral bleeding (Hylek et al. 2007).

ASA, 75 or 325 mg daily, had a protective effect regarding ischemic insults in several studies. However, risk reduction was only about 20% (Hart et al. 1999). The combination of oral anticoagulation and antiplatelet drugs in patients with atrial fibrillation and stable coronary heart disease should be avoided as it leads to more bleeding complications without reduction of vascular events (↓↓) (B) (Akins et al. 2007). The combination of ASA and clopidogrel is less effective than oral anticoagulation with warfarin while having an identical rate of severe bleeding complications (Connolly et al. 2006).

Because the risk for stroke is strongly dependent on the AF-type and the vascular risk profile, a **stratified primary prevention** is recommended:

- In patients younger than 65 years and without further risk factors there is only a low stroke risk with no proven indication for an anti-thrombotic therapy. Optionally, a therapy with ASA can be started.
- Patients younger than 65 years with risk factors or patients in the age of 65–75 years without risk factors have an intermediate risk and should be treated with ASA or oral anticoagulation.
- Patients with a high thrombembolic risk should be permanently anticoagulated.

The BAFTA-study showed that oral anticoagulation is superior to ASA in patients >75 years with atrial fibrillation and that it does not lead to a higher incidence of bleeding complications (Mant et al. 2007). Hart and Halperin (2001) recommend anticoagulation with a target INR of 2–3 until the age of 75 and of 2.0 from there on. The individual stroke risk can best be determined with the CHADS2 score (Gage et al. 2001). However, this is not yet used for stratification regarding anticoagulation or administration of ASA (Fuster et al 2006).

Primary prevention in other cardiac diseases

Patients with a congenital or acquired valvular defect or with mechanical artificial valves benefit from the preventive effect of oral anticoagulation (Cannegieter et al. 1995, Salem et al. 1998). The annual stroke risk is 1–4% in mechanical and 0.2–2.9% in biological prostheses. An INR of 2.5–3.5 is recommended, which, empirically, is a good compromise between an effective thrombotic prevention and avoidance of bleeding complications. Patients with biological valve replacement in the mitral position are anticoagulated for 3 months, and thereafter, treated with ASA. Strokes during acute myocardial infarctions are detected in 2.5% of the cases during the first 6 weeks. Patients with a history of myocardial infarction with a low ventricular function and concomitant atrial fibrillation should be anticoagulated permanently (Hardman and Cowie 1999).

The relevance of a PFO (patent foramen ovale), which is found in 20–25% of all people, is still not completely clear. In patients with an isolated PFO the odds ratio for stroke derived from case control studies is 1.83 (Overell et al. 2000). Presumably, a concomitant septal aneurysm leads to an elevated stroke risk. For primary prevention, neither anticoagulation nor any forms of operative or interventional treatment are indicated. An exception to this is a large defect that is hemodynamically relevant. In this case, the treatment is performed for cardiopulmonary reasons and not for cerebrovascular prevention.

Patients with a mitral valve prolapse do not have an elevated stroke risk and do not need any medical prophylaxis (Gilon et al. 1999).

Operation of an asymptomatic stenosis of the internal carotid artery

The two largest studies on carotid endarterectomy in primary prevention, the ACAS (Asymptomatic Carotid Atherosclerosis Study) from North America which included 1,662 patients (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995) and the ACST (Asymptomatic Carotid Surgery Trial) from Europe which included 3,120 patients (Halliday et al. 2004) could independently show a mild primary preventive effect. The ARR for stroke or death over a period of 5 years was 5.4–5.9%

Table 2 Schema of the evidence and effectiveness of recommended actions in the primary prevention of stroke.

Type of intervention	Level of recommendation	Prevalence in the population	Relative RR per year	Absolute RR per year	NNT	Remarks
Antihypertensive therapy	A	20–40 %	30–40 %	0,5 %	200	Most important preventive action
Atrial fibrillation: anticoagulation	A	1 %	59 %	2.7 %	37	Proven in high risk patients
ASA-Therapy	B		29 %	1.5 %	67	In low or intermediate risk
Statin therapy in hypercholesterinemia	A	5–10 %	20 %	1 %	100	Only in high risk patients Prevention mainly of atherosclerotic manifestations
Operation of asymptomatic carotid stenosis (>60 % ACST)	A	5 %	30–40 %	0.5–1 %	100–200	Only effective if the periprocedural risk is <3 %
Nicotine abstinence	B	20 %	50 %	?	?	Almost no elevated vascular risk after 10 years
Weight normalization	B	20 %	?	?	?	Multidimensional effect
Physical activity	B	–	25–48 %	?	?	At least 1× per week
Antidiabetic therapy	C	3–5 %	?	?	?	Reduction of stroke not convincingly documented
Anticoagulation in other heart diseases	C	<0.1 %	?	?	?	Recommended in patients with artificial heart valves, severe left ventricular dysfunction, valve-vegetation

which equals an annual risk reduction of about 1 % (NNT = 100). The following subgroups benefit according to the larger ACST from an operation:

- Men (absolute RR over 5 years 8.2 %)
- Patients <65 years (7.8 %)
- Patients 65–74 years (7.5 %)
- Patients with a moderate stenosis of 60–80 % (7.4 %)
- Patients with elevated serum-cholesterol >250 mg/dl (11.4 %)

No differences were observed regarding the patient's blood pressure or the ultrasound morphology of the stenosing plaque. Relevance is limited, because the operating surgeons in both studies have been selected by very strict criteria. In the ACAS-study, approximately 10 % of all applying surgeons were rejected because of too high complication rates (Moore et al. 1991). This selection process led to a very low complication rate of 2.3 % (ACAS) and 2.8 % (ACST).

Presumably, the complication rates in unselected surgeons are not always below 3 % (Bond et al. 2003, Bond et al. 2004), so that a potentially preventive effect of the carotid endarterectomy is offset (>3 % complications) or even reversed (>6 % complications). However, the procedural results of operative departments are only comparable if a neurological examination is documented for every patient before and after the procedure. Referring doctors and patients should be aware of this quality characteristic.

Table 2 outlines the recommendations for primary prevention of stroke.

Secondary prevention of ischemic stroke

Aim of secondary prevention is to avoid a second cerebral ischemia (TIA or stroke) after a first event. Data about the prevention of further events (so called tertiary prevention) are mostly gained retrospectively from the results of secondary prevention; there are no specific studies available.

Epidemiology

About 80–85 % of patients survive the acute phase of a first stroke (Grau et al. 2001, Wolf et al. 1992). In 8–15 % of these patients a second event occurs within the first year. The risk is highest within the first weeks and diminishes with increasing time since the index-event (Johnston et al 2000, Weimar et al. 2002, Hill et al. 2004, Lovett et al. 2004). With the third year the combined vascular risk increases again. Patients with multiple vascular risk factors or those with concomitant coronary heart disease or peripheral vascular disease are especially endangered. Regarding TIAs, patients with cerebral symptoms are at higher risk than those with ocular symptoms (amaurosis fugax). The risk after a TIA is also increased in patients older than 60 years, with symptoms lasting longer than 10 minutes, paresis or aphasia. The risk is highest within the first 3 days after a TIA (Giles and Rothwell 2007).

Examinations

Necessary

- Neurological and general physical examination
- CT or MRI (differential diagnosis ischemia, bleeding, SAH etc.)
- Ultrasound of the brain supplying arteries (if result is inconclusive: CTA or MRA)
- Blood tests
- ECG
- Echocardiography (in case of territorial infarction)

Required in individual cases

- 24-hour-ECG
- 24-hour-blood pressure measurement
- Special blood tests (exclusion of vasculitis, blood coagulation disorder)

Treatment of risk factors

Recommendations

- Antihypertensive therapy reduces the stroke risk (A). As the benefit concerns both patients with and without hypertension this recommendation is true for all patients after TIA or stroke (B).
- Which substance class is most effective in secondary prevention of stroke is still subject for discussion. The combination of perindopril and indapamid is significantly more effective than placebo (A), and eprosartan is significantly more effective than nitrendipine (A). Ramipril reduces the risk of vascular events in patients after stroke (B).
- The early secondary prevention of the ischemic insult with telmisartan in addition to a common antihypertensive therapy showed no superiority to placebo (A).
- However, probably all antihypertensive drugs are effective in secondary prevention of stroke (B). Beta blockers (atenolol) seem to be less effective (B). To reach the therapeutical aim (normal blood pressure) is, like in primary prevention, more important than the type of antihypertensive agent that is used. To achieve this, in the majority of patients a combination therapy is necessary.
- Concomitant diseases (CHD, diabetes, renal diseases) should be considered in the choice of substance class (C). According to the data of the MOSES-study, the ideal systolic blood pressure is between 120 and 140 mm Hg.
- Modification in lifestyle can lead to a reduction of blood pressure and should supplement the medical therapy (C).
- In patients with a focal cerebral ischemia, statins should be used irrespective of the base LDL-cholesterol level (A). The aimed level should be between 70 and 100 mg / dl. In patients with ischemic TIA / stroke (mod. Rankin < 3) and without coronary heart disease with LDL-C-levels between 100 and 190 mg / dl, 80 mg of atorvastatin per day is effective for reduction of the risk for recurrent stroke and cardiovascular morbidity (A). The reduction of LDL-C-level, however, is probably more important than the use of a certain statin (C). It is therefore recommended to reduce the LDL-C-level to below 100 mg / dl with the use of any statin. The benefit of this treatment is most noticeable if the base LDL-C-level is reduced by ≥ 50 %. In patients with a haemorrhagic TIA / stroke a prophylaxis with atorvastatin should only be carried out only in exceptional cases (for instance out of cardiovascular indication) (B).
- The treatment of hyperhomocysteinemia with vitamin B6, B12 and folic acid is not effective (A).
- A hormone replacement therapy after the menopause is not effective as secondary stroke prevention (B).

Hypertension

There is clearly more data available about effectiveness of antihypertensive therapy for primary prevention of cardio- and cerebrovascular events than for secondary prevention. Available data does not answer the effectiveness of different substance classes. A meta-analysis included 7 randomised controlled studies with 15,527 patients after cerebral infarction, TIA and cerebral haemorrhage, who had been randomised between 3 weeks and 14 months after the event, and had been monitored for 2–5 years. Reduction of blood pressure or the treatment of arterial hypertension reduced the stroke risk by 24 %, the risk for nonfatal stroke by 21 % and the risk of myocardial infarction by 21 % (Rashid et al. 2003). According to this meta-analysis a better effectiveness was found for the combination of ACE-inhibitor and diuretic (− 45 %) than diuretics alone (− 32 %), ACE-inhibitor alone (− 7 %) or beta blocker (− 7 %, not significant) concerning the endpoint stroke (Rashid et al. 2003).

Because of possible additive pleiotropic and vascular effects, the role of ACE-inhibitors and sartans are subject for discussion. The Heart Outcomes Prevention Evaluation (HOPE) study compared the ACE-inhibitor ramipril to placebo. In the subgroup of 1,013 patients with a history of cerebral infarction or TIA, a relative risk of 24 % was found for reduction of the endpoint stroke, myocardial infarction or vascular death. For the observation period of five years this is equivalent to an absolute risk reduction of 6.3 % (Flather et al. 2000).

PROGRESS was the first big randomised study for antihypertensive therapy in secondary prevention after stroke or TIA. In this study 6,105 patients were treated with either the ACE-inhibitor perindopril as a single treatment or in combination with the diuretic indapamid or placebo. After an observation period of 4 years a reduction of 9 / 4 mm Hg was found. For the endpoint stroke the absolute risk reduction was 4 %, and the relative risk reduction was 28 % ($p < 0.0001$). Also the number of vascular events could be lowered relatively by 26 %. Interestingly, both hypertensive and non-hypertensive patients had comparable benefit from the treatment, though in a very high limit of 160 / 90 mm Hg. The combination of the ACE-inhibitor and a diuretic showed to be especially effective. The stroke rate was relatively reduced by 43 %. Perindopril alone was not significantly more effective than placebo. However, in the combination treatment group the patients were younger, the proportion of male patients and patients with hypertension or CHD was higher and the patients were randomised earlier (Progress Collaborative Group 2001).The blood pressure reduction was decidedly higher in the combination group so that the difference in the primary endpoints probably primarily results from the blood pressure reduction itself and not from the combination per se. This underlines once again the outstanding importance of blood pressure reduction in secondary prevention.

In the placebo-controlled Phase-II-study ACCESS, the AT1-blocker candesartan was evaluated in 342 patients with an explicit hypertension (> 200 / 110 mm Hg) in the early phase after a stroke with motor deficit. In the first 7 days the patients double-blindly received either candesartan or placebo. Thereafter, all patients were treated with candesartan. After 12 months the rate of vascular events differed significantly in the candesartan- and placebo-group (9.8 % vs. 18.7 %, RRR 52 %). However, it is difficult to understand how a 7 day treatment in the early phase can cause such a difference (Schrader et al. 2003). The ACCESS-study was designed as a safety-study in the acute-phase and not as a study for secondary prevention.

In the MOSES-study 1,352 patients were included who had arterial hypertension that needed treatment and who had suffered from either stroke or TIA within the last 24 months. The patients were included after an average of 12 months. After an open randomisation they were treated with either the AT1-antagonist eprosartan (600 mg) or the calcium-antagonist nitrendipine (10 mg). The endpoint-analysis was done blinded. After a mean 2.5 years of observation period, 13.3 vascular events (stroke, myocardial infarction, vascular death) occurred in the eposartan-group per 100 patient-years versus 16.7 in the nitrendipine-group (Schrader et al. 2005). The optimal systolic blood pressure in the MOSES-study during treatment was between 120 and 140 mm Hg.

In the PRoFESS-study 20,332 patients with an ischemic stroke were treated with 80 mg telmisartan or placebo for an average time period of 2.4 years in addition to the regular antihypertensive treatment. Half of the patients were included within the first 15 days after the initial event. A positive trend was seen for telmisartan regarding the endpoints recurrent stroke and the combination of stroke, myocardial infarction and vascular death. This trend however was not significant.

Hypercholesterinemia

Even though the association between total cholesterol or LDL-cholesterol and stroke is not as clear as in coronary heart disease, numerous studies have shown that statins lower the stroke risk in patients with vascular diseases, especially in patients with CHD (Paciaroni et al. 2007). Large meta-analyses found a relative risk reduction of about 21 % (Amarenco et al. 2004). According to the NCEP-ATP-III-guidelines, stroke patients with a manifest CHD (or vascular disease with an equivalent risk) should be treated with a statin. The aimed LDL-C-level should be < 100 mg / dl or < 70 mg / dl (↑↑) in high risk patients with multiple risk factors (A) (Grundy et al. 2004).

Patients after stroke / TIA and without a manifest CHD were investigated in a subgroup of the Heart Protection Study (HPS) as well as in the SPARCL-study. Within the HPS-collective of 20,536 high risk patients, 3,280 with stroke / TIA were included, 1,820 of these without CHD. These patients, similar to the entire study population, showed a high absolute vascular risk of 29.8 % over 5 years which was reduced by simvastatin to 24.7 % (RRR 20 %, ARR 5.1 %, NNT 20 / 5 years) (Heart Protection Study Collaborative Group 2002). While in the entire group the stroke risk was reduced by 25 % (RR) analogue to the other vascular endpoints, surprisingly no effect on stroke risk could be found in the subgroup of stroke patients (Collins et al. 2004). Less ischemic brain-infarcts were found (100 versus 122) but twice as many bleedings (21 versus 11). In the SPARCL-study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) 4,731 patients with TIA / stroke without additional CHD and LDL-C-levels between 100 and 190 mg / dl were treated with 80 mg of atorvastatin versus placebo (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels [SPARCL] Investigators 2006). After a mean of 4.9 years, the primary endpoint (fatal or non-fatal stroke) was significantly reduced with atorvastatin treatment (11.2 % vs. 13.1 %, RRR 16 %, ARR 2.2 % per 5 years). The differences between HPS and SPARLC regarding recurrent strokes might be explained by a difference in time intervals from the index event, which was 4.3 years on average in HPS, but maximal 6 months in SPARCL. If coronary events and vascular death were considered in addition, the combined vascular endpoint in SPARCL was significantly reduced by 20 % (relative), respectively 3.5 % (absolute) per 5 years (NNT 29 per 5 years). Ischemic brain infarctions were significantly reduced during atorvastatin treatment (218 versus 274 events) while haemorrhagic strokes occurred significantly more often (55 vs. 33). However, no relation was found to the atorvastatin treatment or to the basic- or treatment-levels of LDL-C. Male patients in higher age with a haemorrhagic first stroke and distinctive high blood pressure had a significant higher risk for a second haemorrhagic event (Goldstein et al. 2007). Treatment with statins should be started in this subgroup only because of other indications (CHD, LDL-C > 190 mg / dl). Another analysis of SPARCL shows that the protective effect of stroke risk reduction is best if a reduction in LDL-C of ≥ 50 % is achieved (Amarenco et al. 2007). If, under this consideration, a modification in dosage and selection of statin (for instance for financial reasons) is possible cannot be answered. However, it is assumable for secondary prevention in cardiovascular diseases according to the data from similar studies.

Generally, the statin therapy should begin as soon as possible after admission to the hospital. There are some hints that discontinuing the statin therapy in patients with an acute vascular event is associated with a higher morbidity and mortality (Endres and Laufs 2006; Blanco et al. 2007). Therefore, patients who took statins before the stroke should receive the medication also on day of admission and thereafter (↑) (B).

Diabetes mellitus

Results for diabetes treatment with glitazone in secondary stroke prevention showed no difference regarding macrovascular complications in comparison to placebo (Wilcox et al. 2007).

Hyperhomocysteinemia

The VISP-study showed no benefit from therapy with B-vitamins and folic acid in stroke patients with elevated homocysteine levels (Toole et al. 2004). Also, two newer studies show that a therapy with vitamin B6, B12 and folic acid is capable of lowering the homocysteine level, but is not able to prevent cerebrovascular or cardiovascular diseases. The Norwegian Vitamin Study (VORVIT) showed that in 3,749 patients after a myocardial infarction who were treated early after the event (< 7 days) with either placebo or 0.8 mg of folic acid, 0.4 mg of vitamin B12 and 40 mg of vitamin B6 four times a day, the homocysteine levels fell by 27 % in those that had received folic acid and vitamin B12. This, however, had no effect on the occurrence of the primary endpoint (combined heart attack, stroke or vascular death during an observation period of 40 months). In contrast, patients who received vitamin B12, B6 and folic acid showed a trend to reach this primary endpoint even more likely (+ 22 %). How much these results do also apply to strokes is not clear at this point. The analysis of the results of the HOPE-2-study (The Heart Outcomes Prevention Evaluation [HOPE] 2 Investigators 2006) showed contradictory results in 5,522 patients older than 55 years with a previous vascular event or diabetes mellitus. The patients were treated with either placebo or 2.5 mg of folic acid, 50 mg of vitamin B6 and 1 mg of vitamin B12 for 5 years. Again significant lowering of homocysteine levels was detected. However, the primary endpoint (combination of vascular death, heart attack or stroke) was not reached (RRR 5 %). But significantly fewer patients had a stroke during the vitamin therapy (– 25 %). The NNT for a vitamin therapy is 800 to prevent one stroke per year. In combination with the earlier published VISP-study there is no recommendation at this moment for treating an elevated homocysteine level with a vitamin therapy. A big Australian study (VITATOPS) will provide additional data in the next years.

Postmenopausal hormone replacement therapy

A study by Viscoli et al. (2001) showed an increase of fatal strokes and a worse prognosis regarding disability in nonfatal strokes for female patients in postmenopausal hormone replacement therapy (HRT). The authors conclude that the HRT after a stroke is not helpful but rather relatively contraindicated because of the worse prognosis.

Secondary prevention with antiplatelet drugs

Recommendations

- In patients with a focal ischemia, antiplatelet drugs are effective in secondary prevention (A). This is true for ASA (50–150 mg) (A), the combination of ASA (2 × 25 mg) and slow-release dipyridamole (2 × 200 mg) (A) and clopidogrel (75 mg) (B).
- In patients after TIA and ischemic insult with a low risk for recurrent stroke (< 4%) the daily administration of 100 mg of acetylsalicylic acid is recommended (A).
- In patients with a high risk for recurrent stroke (≥ 4%) a fixed combination of 25 mg ASA and 200 mg slow-release dipyridamole twice daily or clopidogrel 75 mg is recommended (A).
- In patients with contraindications or intolerance of ASA, clopidogrel 75 mg is recommended (A).
- The combination of slow-release dipyridamole and ASA in secondary stroke prevention is just as effective as a single treatment with clopidogrel (A).
- In patients that suffer from a stomach- or duodenal ulcer during ASA therapy, a continuation of the ASA-prophylaxis in combination with a proton pump inhibitor after a healing period is recommended (B).
- ASA in doses > 150 mg cause a higher risk for bleeding complications (B).
- The combination of 75 mg ASA and 75 mg clopidogrel is not more effective than the single treatment with clopidogrel; ASA, however, causes more bleeding complications (A).
- The duration of a treatment with antiplatelet drugs for a period of more than 4 years after the initial event has not been investigated yet. Theoretically, however, the prophylaxis should be continued for the rest of the life if tolerated (C).
- If a second ischemic event occurs during ASA-therapy, pathophysiology and recurrent stroke risk should be evaluated again. If a cardiac source for emboli is found, oral anticoagulation is indicated. If the recurrent stroke risk has not changed, the prophylaxis with ASA can be continued (C). If the recurrent stroke risk has increased, the treatment is readjusted to a combination of ASA and slow-release dipyridamole or to clopidogrel (C).
- Patients with TIA or stroke and an acute coronary syndrome should be treated with a combination of 75 mg of clopidogrel and 75 mg of ASA over a period of 3 months (C).

A major point in secondary stroke prevention is the intake of antiplatelet drugs. Several meta-analyses showed its essential part in stroke prevention (Antiplatelets Trialists' Collaboration 1994, Antithrombotic Trialists' Collaboration 2002, Born and Patrono 2006). The only lack of clarity lies in the dosage and type of medication. Meta-analyses showed that the risk of a nonfatal stroke could be reduced by 23% (from 10.8% to 8.3% over 3 years) in patients after TIA or stroke, using an antiplatelet drug (Antithrombotic Trialists' Collaboration 2002). The combined vascular endpoint (stroke, myocardial infarction, vascular death) is reduced by 17% (from 21.4% to 17.8% over 29 months) (↑↑).

Acetylsalicylic acid (ASA)

A total of 11 placebo controlled studies about ASA as secondary prevention after TIA or stroke are available. A meta-analysis showed a relative risk reduction of 13% (95% CI 6–16%) for a combined vascular endpoint (vascular death, stroke, myocardial infarction) (Algra and van Gijn 1999). Several meta-analyses could not demonstrate a difference for the distinct dose intervals (Algra and van Gijn 1999, Antithrombotic Trialists' Collaboration 2002, Patrono et al. 2005). At this point, in Germany, like in most other European countries, a therapy with 100 mg of ASA per day has been established. It is important to know that both the subjective gastrointestinal side effects (such as nausea, dyspepsia etc.) as well as bleeding complications are dose dependent (Yusuf et al. 2001, Topol et al. 2003). In ASA-doses of > 150 mg / day the risk of bleeding complications increases significantly (Topol et al. 2003). In patients that develop side effects during ASA therapy, clopidogrel can be used (see below). In cases of gastric or duodenal ulcers during ASA intake, a continuation of the ASA treatment in combination with a proton pump inhibitor after a healing period causes less bleeding complications than treatment with clopidogrel without a proton pump inhibitor (Chan et al. 2005) (↑). The combination of a proton pump inhibitor and clopidogrel has not yet been investigated.

Clopidogrel

Clopidogrel has been investigated in nearly 20,000 patients in the CAPRIE-study (CAPRIE Steering Committee 1996). The primary end point, a composite outcome of myocardial infarction, ischemic stroke, or vascular death occurred in 8.7% fewer patients treated with clopidogrel compared with ASA ($p < 0.043$). The absolute annual risk reduction was 0.51% per year. The benefit in the 3 disease subgroups of the study (myocardial infarction, stroke and peripheral artery disease) seems not to be identical. Patients with PAD (23.8%) or PAD plus stroke plus myocardial infarction (22.7%) who were treated with clopidogrel had a greater risk reduction. The rate of gastrointestinal bleedings was significantly lower in the clopidogrel-group than in the ASA-group (1.99 vs. 2.66%). Gastrointestinal side effects were significantly less frequent during the intake of clopidogrel than ASA (15% vs. 17.6%)

In the MATCH-study, the prophylactic efficacy of clopidogrel in comparison to the combination of clopidogrel plus 75 mg of ASA in high risk patients with a previous TIA or ischemic stroke was investigated (Diener et al. 2004a). Primary endpoint was the occurrence of myocardial infarction, stroke or vascular death or admission to the hospital due to a second vascular event. During the evaluation period of 18 months no statistically significant difference regarding this endpoint was found. However, there was a significant difference in the rate of bleeding complications: life-threatening bleeding complications were significantly more frequent in the combination group (2.6% vs. 1.3%).

In the CHARISMA-study (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) it was investigated if the combination of clopidogrel and ASA would be an advantage to ASA alone in the treatment of atherothrombotic risk patients (Abou-Chebl et al. 2004). CHARISMA included a primary prophylaxis arm in patients with multiple risk factors and 3 secondary prophylaxis cohorts (cardiovascular, cerebrovascular, symptomatic peripheral arterial occlusive disease). The participants were treated with either ASA (75–162 mg) or a dual platelet inhibition with ASA and 75 mg of clopidogrel. 15,603 patients from 32 different countries were included, out of whom 1,233 patients had suffered a TIA and 3,245 an ischemic stroke. The median evaluation period was 28 months. Primary endpoint was the first occurrence of either myocardial infarction, stroke of any cause (incl. intracerebral bleeding) or a vascular death.

In the total population a non significant relative risk reduction of 7.1% of the primary endpoint was found in favour of the dual platelet inhibition (6.8% for dual platelet inhibition vs. 7.3% for ASA-monotherapy; $p = 0.22$). In terms of endpoint events there were more strokes ($n = 334$) than myocardial infarctions ($n = 306$). Con-

cerning cerebrovascular events, there was a trend in favour of dual platelet inhibition. Nonfatal strokes occurred in 149 (1.9%) patients in the dual platelet inhibition group and in 185 (2.4%) patients in the ASA group (RR 0.80, CI 0.65–0.997; p=0.05). A smaller difference was found for nonfatal ischemic strokes: 132 (1.7%) in the dual platelet inhibition group and 160 (2.1%) in the ASA-group (RR 0.82%; CI 0.66–1.04; p=0.10). The risk for major bleeding for the total population was 1.7% in dual platelet inhibition and 1.3% in ASA-monotherapy. Primary intracerebral bleedings occurred in 26 (0.3%) patients with dual platelet inhibition and in 27 (0.3%) of the ASA-group (p=0.89). A significant difference was found in the rate of moderate bleedings: 164 (2.1%) patients with dual platelet inhibition and 101 (1.3%) of the patients in the ASA-group had a moderate bleeding complication (p<0.001).

An analysis of the subgroups showed an increased relative risk for primary endpoint events in the primary prevention group with dual platelet inhibition of 20% (6.6% versus 5.5%; p=0.20). The rate of major bleedings did not differ significantly (2.0% vs. 1.2%; p=0.07), however the mortality did (5.4% vs. 3.8%; p=0.04). In the group of symptomatic patients, on the other hand, a relative risk reduction of 12% was found due to dual platelet inhibition (6.9% vs. 7.9%; p=0.046). In the group of cerebrovascular patients the relative risk reduction was especially high: 16% (p=0.09). Neither the number of major bleedings (1.6% vs. 1.4%; p=0.39) nor the mortality (4.6% vs. 5.0%; p=0.27) were significantly different in the secondary prevention group (Bhatt et al. 2007).

Dipyridamole

Dipyridamole is the third clinical relevant antiplatelet drug. The first placebo controlled European study (ESPS-1) published results in 1987 with 2,500 patients who had suffered a stroke or TIA (The ESPS Group 1987). One group of patients received 990 mg ASA and 225 mg of dipyridamole daily, the other group received placebo. The primary endpoint was stroke or death of any reason. This endpoint was lowered by 33% over two years in the verum group. The largest study until today was ESPS-2 with 6,602 patients (Diener et al. 1996). This study had 4 arms: ASA (2×25 mg/d), slow-release dipyridamole (2×200 mg/d), ASA plus slow-release dipyridamole (2×25 mg/d+2×200 mg/d) and placebo. The qualifying event was either stroke or TIA. The primary endpoint was stroke and/or death within 2 years. The combined therapy showed in comparison to ASA a relative risk reduction of 23% (3% absolute) for the endpoint recurrent stroke and compared to placebo a relative risk reduction of 37% (5.8% absolute) while ASA alone lead to a stroke risk reduction of 18% (2.9% absolute) and dipyridamole alone of 16% (2.6% absolute). Concerning the endpoint „stroke and death" the risk reductions were 13% (2.6%), 24% (5.6%), 13% (3%) and 15% (3.5%). Substantial bleeding complications occurred in the group treated with the combination and in the group treated only with ASA in 8.7% and 8.3%, respectively. This rate was 4.7% in the dipyridamole group and 4.5% in the placebo group. Headache was the reason for discontinuing the treatment in 8.1% of patients in the combined therapy arm, in 8% of patients treated only with dipyridamole, in 1.9% of patients treated only with ASA and in 2.4% in the placebo arm. Cardiac events were not more frequent in the dipyridamole-group than the group treated with ASA (Diener et al. 2001).

In the industry-independent ESPRIT-study (The ESPRIT Study Group 2006), 2,739 patients with a TIA or minor stroke, presumably due to an atherosclerotic cause were included and treated with ASA (30–325 mg/d). Out of these, 1,376 patients additionally received dipyridamole, in 83% in a slow-release formulation (200 mg twice daily). The study was designed open, but the endpoint was evaluated blinded (PROBE-Design). Primary endpoint was the combination of clinically manifest events (vascular death, stroke, myocardial infarction, major bleeding). The mean observation period was 3.5 years, the mean ASA-dose 75 mg in both groups. The event rate regarding the primary endpoint was significantly higher in the ASA-single treatment regiment arm (16%) than in the combination therapy (ASA plus dipyridamole) (13%). The difference equals a relative risk reduction of 20%. The absolute risk reduction was 1% per year. Regarding the safety endpoints the rate of bleeding events in the combination therapy (2.6% vs. 3.9%) and the rate of cardiac events (3.2% vs. 4.4%) did not differ significantly to the ASA treatment alone. It is worth mentioning the difference in the number of patients that discontinued treatment: 34% of the patients in the combination arm stopped treatment (mostly because of headache) in comparison to 13% in the single treatment arm (mostly because of ischemic events).

In a recent meta-analysis of the available studies including the ESPRIT-results as well as the ESPS-2 study, a significant relative risk reduction regarding the combined vascular endpoint of 18% (95% confidence interval 9–26) was calculated for the combination of ASA plus dipyridamole compared to ASA alone.

The PRoFESS-study directly compared clopidogrel and the combination of ASA and dipyridamole (Diener et al. 2007). In this study 20,332 patients with an ischemic insult were treated with ASA plus slow-release dipyridamole or clopidogrel over a mean period of 2.4 years. No significant difference regarding the effectiveness was found for any of the primary or secondary endpoints. The combination of ASA and dipyridamole had a tendency to lead to more severe bleeding complications and more frequently to discontinuation of the treatment due to headache.

GP-IIb/IIIa-antagonists

Glycoprotein-IIb/IIIa-receptors belong to the group of plasma membrane receptors (integrins). They are only found on thrombocytes and their precursors. The inhibition of these receptors keeps the platelets from aggregation and inhibits the creation of fibrinogen bridges. There are three intravenous GP-IIb/IIIa-inhibitors available: abciximab, eptifibatid and tirofiban. In the acute coronary syndrome they have shown to be effective and reduce the early mortality (Topol et al. 1999). In stroke patients early data for the use of abciximab had indicated a safe use (Burton 2003). A phase-III-study, however, had to be stopped due to an increased bleeding rate and no sufficient efficacy (Adams et al. 2008). For the competitive receptor antagonist tirofiban until now only smaller studies without safety concerns are available, also in combination with rtPA (Junghans et al. 2001, Seitz et al. 2003) – further studies are pending (SATIS). However, one has to assume that in these studies the bleeding complications will outweigh the therapeutical benefit, too.

All studies that investigated oral glycoprotein-IIb/IIIa-inhibitors in secondary stroke prevention had to be stopped due to an increased bleeding rate (BRAVO) (Topol et al. 2003). Therefore, GP-IIb/IIIa-antagonists should not be used in secondary stroke prevention. They are not more effective than acetylsalicylic acid. Their use, however, is accompanied by a significantly increased bleeding risk.

Table 3 sums up the relative and absolute risk reductions for the antiplatelet drugs. For calculation of recurrent stroke risk,

Table 3 Schema of different steps in stroke prevention after TIA or first stroke.

Type of Intervention	Level of recommendation	Relative RR	Absolute RR per year	NNT per year	Remarks
Antihypertensive therapy	A	24 %	0.46 %	217	Well documented for perindopril, indapamid and eprosartan
Statins after TIA and Insult	A	16 %	0.4 %	250	Until now documented for atorvastatin and simvastatin
ASA 50–150 mg in TIA or ischemic insult	A	18–22 %	1.3 %	77	ASA-doses > 150 mg = higher bleeding risk
ASA 50 mg + Dipyridamole 400 mg vs. ASA	A	23 %	1.0–1.5 %	33–100	Combination also significantly more effective than placebo
Clopidogrel vs. ASA	B	8 %	0.5 %	200	Based on a subgroup analysis of the CAPRIE-study
Operation of a high-grade carotid artery stenosis *	A	65 %	3.1 %	32	More effective if the operation is within the first 4 weeks after the event
ASA in high-grade intracranial stenosis	B	?	?	?	Only investigated in comparison to warfarin
Oral anticoagulation in cardiac source of emboli (AF); aimed INR = 3.0	A	68 %	8 %	12	Until now only tested against placebo in one study
ASS in cardiac source of emboli	A	19 %	2.5 %	40	In contraindications for oral anticoagulation

* Endpoint stroke and death; NNT = number needed to treat; RR = risk reduction compared to ASA; AF = atrial fibrillation

Table 4 Model for risk evaluation of a recurrent insult after a first ischemic event, based on the Essen Risk Score. A score of ≥ 3 points means a recurrent stroke risk of ≥ 4 % per year.

Risk factor	Points
< 65 years	0
65–75 years	1
> 75 years	2
Arterial hypertension	1
Diabetes mellitus	1
Myocardial infarction	1
Other cardiovascular events (w / o myocardial infarction and atrial fibrillation)	1
Peripheral artery disease	1
Smoking	1
Additional TIA or insult to the qualifying event	1

Table 5 ABCD 2-score for risk evaluation after prior TIA. Patients with up to 3 points have a low 2-day risk (1 %) for stroke. Affected patients with a score of 4 or 5 points have a medium risk (4.1 %). A score of 6 or 7 points means a high stroke risk of 8.1 %.

	ABCD-2-Score
A	Age: one point for patients aged 60 or more
B	Blood pressure: higher than 140 / 90 mm Hg: If yes, one point
C	Clinical features: 2 points for a unilateral weakness, one point for speech disturbance without weakness
D	Duration of symptoms: duration of symptoms between 10 and 59 minutes means one point, duration longer than 60 minutes means 2 points
D	Diabetes: positive history for diabetes mellitus, one point

the meanwhile positively validated Essen Risk Score is used (**Table 4**) (Diener 2005, Diener et al. 2005, Weimar et al. 2007). The risk assessment after TIA using the ABCD 2-score is shown in **Table 5**.

Anticoagulation in cardiogenic thrombembolic events

Recommendations

- In patients with a cardiac source for emboli, especially with atrial fibrillation, oral anticoagulation with an INR of 2–3 is recommended (A).
- If there are contraindications against oral anticoagulation, 300 mg of ASA is recommended, like it is suggested in primary prevention (B). However, it is to expect that 100 mg is effective likewise.
- In patients with a mechanical heart valve replacement, anticoagulation with INR-levels between 2.0 and 3.5 is continued (C).
- After TIA or minor stroke and atrial fibrillation, oral anticoagulation can be started within the first week (C).
- In patients with a biological valve, temporary anticoagulation for 3 months is recommended (C).
- The combination of ASA and clopidogrel is inferior to oral anticoagulation and shows a similar rate of severe bleeding complications (B).

The evidence for oral anticoagulation in stroke patients with atrial fibrillation relies mainly on the European Atrial Fibrillation Trial (EAFT Group 1993). This randomised study, published in 1993, could demonstrate a relative risk reduction of 68 % for a recurrent stroke compared to 19 % under therapy with 300 mg ASA in patients with stroke and atrial fibrillation. Most patients, however, were included weeks (up to 3 months) after the qualifying event. The NNT to prevent a stroke, myocardial infarction or vascular death was 12 per year so that this seems to be the most effective prophylaxis after stroke (EAFT Group 1993). A Cochrane analysis of this study as well as a randomised Italian study

showed that oral anticoagulation is more effective than antiplatelet drugs. This is true for vascular events (OR 0.67; 95% CI 0.50–0.91) as well as recurrent strokes (OR 0.49; 95% CI 0.33–0.72). Although the risk for extracranial bleedings was significantly elevated during oral anticoagulation, this was not the case for intracranial bleedings (Saxena and Koudstaal 2004). It is to expect that patients with intermittent atrial fibrillation have benefit as well. According to the Euro Heart Survey on AF (EHS-AF) these patients showed a similarly high risk for stroke as patients with chronic atrial fibrillation (Hart et al. 2000a, Nieuwlaat et al. 2005). As the ideal target INR for oral anticoagulation a value of 2–3 is recommended (Fuster et al. 2006). In INR-values of >3, there is a steep increase in bleeding risk (Hylek et al. 2007).

The only ASA dose which is studied in atrial fibrillation, was 300 mg. In analogy to ischemic stroke prevention of other aetiology, however, a dose of 100 mg should be sufficiently effective. In patients with mechanical heart valves or other high risk findings the INR should be up to 3.5. In a meta-analysis of 21 studies, including 6,248 patients with atrial fibrillation, an INR of <2 was associated with an OR of 5 for ischemic strokes and an INR of >3 with an OR of 3 for haemorrhagic strokes compared to an INR of 2–3 (de Lemos at al. 2004).

Currently, the WARCEF-study investigates oral anticoagulation versus ASA in patients with decreased ejection fraction. Results, however, are not expected until a few years from now.

For other cardiac high risk findings like cardiac or aortic thrombus, there are no randomised therapy studies available regarding secondary stroke prevention. In these patients the indication and intensity of long-term anticoagulation is mostly based on a cardiologic point of view. There is almost no evidence for the correct time to start oral anticoagulation after stroke. In spite of a stroke risk of 5% within the first 2–4 weeks, anticoagulation with heparin was not more effective than ASA (Fiebach et al. 2002). Oral anticoagulation in large cerebral infarcts should be delayed several weeks after the event. The use of iv heparin in the acute phase is only indicated when there is proof of a cardiac or aortic thrombus as well as heart valve replacements and must also be weighed against the bleeding risk. After minor stroke and TIA oral anticoagulation may be started within the first week, although there are no clinical studies for this recommendation.

The results of the ACTIVE-W-Study, a combined primary and secondary prevention study, are described in the primary prevention section.

Anticoagulation in non-cardiogenic cerebral ischemia

Recommendations

- Oral anticoagulation after TIA or ischemic insult is not more effective than the administration of ASA and can therefore not be recommended in general (A).
- In a proven dissection of the extracranial brain supplying arteries a temporary anticoagulation for approximately 6 months is recommended (C). Superiority to antiplatelet drugs, however, is not proven.
- In younger patients with an otherwise cryptogenic stroke and protein-C, -S- or antithrombin deficiency or homozygous factor-V-(Leiden)-mutation permanent anticoagulation is recommended (C).

The SPIRIT-Study (Stroke Prevention in Reversible Ischemia Trial) investigated high dose anticoagulation with an INR of 3–4.5 versus 30 mg of ASA daily in patients without a cardioembolic stroke cause (The Stroke Prevention in Reversible Ischemia Trial [SPIRIT] Study Group 1997). The study was stopped due to an increased bleeding rate during oral anticoagulation. For each INR elevation of 0.5, the bleeding risk increased by the factor 1.43 (95% CI 0.96–2.13). Also, more recent data document the lack of superiority of oral anticoagulation compared to ASA in the prevention of secondary events after non-cardiac cerebral insults. The Warfarin ASA Recurrent Stroke Study (WARSS) showed an almost identical rate of ischemic stroke and bleedings during both ASA-intake and oral anticoagulation (INR 1.4–2.8) in patients with an ischemic insult and no cardiac source for emboli (Mohr et al. 2001). This discrepancy can be explained by the different intensity of anticoagulation: if a more intense anticoagulation is chosen, like in SPIRIT, this leads to noticeable more bleedings. At an INR of about 2, bleedings occur similarly often under coumadins and ASA. In the WARSS-study 1.5% severe bleeding complications were observed in patients taking ASA.

With special anticoagulation training and supervision a clear reduction in bleeding complications can be achieved (Ansell et al. 2001, Singer et al. 2004). When educating patients, a rate for severe bleeding complications (including intracerebral bleedings) of 2% per year and 0.5% anticoagulation related deaths should be assumed.

In a Cochrane analysis of 5 randomised studies in patients with TIA or minor stroke due to non cardiac cause, no significant difference was found between antiplatelet drugs and oral anticoagulation of different intensity. Neither did the bleeding rates differ significantly between the low (INR 1.4–2.8) and moderate (INR 2.6–3.6) dose group and the antiplatelet drug group (Algra et al. 2006).

The European-Australian Stroke Prevention Trial (ESPRIT) compared anticoagulation (INR 2.0–3.0) to ASA (30–325 mg) in patients with TIA or minor stroke. The study showed a reduction in recurrent insults during warfarin therapy. However, this advantage was balanced by an increased number of intracerebral bleedings (The ESPRIT Study Group 2007).

In the Antiphospholipid Antibodies and Stroke Study (APASS) no significant difference could be shown for a secondary prophylaxis with warfarin in comparison to ASA in patients with an antiphospholipid-antibody-syndrome (Hacke et al. 2004). Also, independently from secondary prophylaxis, no difference was found in comparison to patients without antiphospholipid antibodies so that these do not seem to be prognostically relevant. There are no randomised studies available that investigate secondary stroke prevention for any other blood clotting disorder. The evidence for anticoagulation in patients with protein C, -S or antithrombin deficiency as well as homozygous factor V (Leiden) mutation is based on studies on patients with a deep vein thrombosis or pulmonary embolism and not on studies with stroke patients.

Also, no randomised studies exist regarding secondary prophylaxis in dissections of the brain supplying arteries. A Canadian observational study including 116 patients with angiographically confirmed acute dissection of the vertebral artery or the carotid artery reported TIAs, strokes or deaths in 17 patients (15%) within the first year. Recurrent strokes occurred within the first weeks after the initial event. The event rate was 8.3% during anticoagulation and 12.4% when taking ASA (not significant) (Beletsky et al. 2003). A Cochrane-Review of 26 observational studies including 327 patients did not show a significant difference in death or disability between oral anticoagulation and antiplatelet drugs (Lyrer and Engelter 2004). Increasing wall haematoma was reported. Still, in dissections with proven embolism a temporary anticoagulation within the first 6 months can be reasonable if

findings in Doppler and duplex-ultrasound, magnet resonance imaging or computed tomography are taken into account (B).

Symptomatic carotid stenosis: carotid endarterectomy (CEA) and stent-supported angioplasty (CAS)

Recommendations

- To confirm the diagnosis of a carotid stenosis, neurological ultrasound techniques, MR- or CT-angiography are sufficient (A). DSA normally is not necessary (B).
- In high-grade stenosis carotid endarterectomy (CEA) should be performed (A). The benefit of the operation is higher in a stenosis of 70 to 95%. In non disabling stroke, the operation should be performed as early as possible, as the risk for recurrent stroke is especially high within the first weeks.
- The benefit of an operation is less in stenosis of 50–70%, in subtotal stenosis (so called pseudo-occlusion), in women and if the operation is performed more than 12 weeks after the index event (B).
- The benefit of the operation is no longer present if the complication rate is >6%.
- The time between the event and the operation should be bridged with antiplatelet drugs. ASA should be continued before, during and after the operation (B). Clopidogrel should be substituted by ASA at least 5 days prior to the operation (C).
- Carotid endarterectomy is at present the first choice therapy of high-grade symptomatic carotid stenoses (A). Carotid angioplasty and stenting is not a routine procedure yet. The stent-supported carotid angioplasty in comparison to the surgical treatment of the symptomatic carotid stenosis has a slightly higher short-term risk (30 days) regarding the periprocedural risk (A). The use of protection devices does not lower the complication rate (B). The complication rates of both treatments vary greatly. Therefore the individual complication rate of the therapist must influence the decision for the type of treatment. In patients older than 65–68 years, the operative therapy has a lower complication rate than stenting. The long-term results (2–4 years) regarding the incidence of a second stroke are identical for both techniques. The restenosis-rate is higher after stenting.
- After stent implantation, a combination of clopidogrel (75 mg) and ASA (100 mg) for 1–3 months is recommended (B).

The indication for surgical treatment of symptomatic carotid stenoses is based on two big prospective randomised international multi-centre studies (NASCET in the USA and Canada, ECST in Europe) (European Carotid Surgery Trialists' Collaborative Group 1991 and European Carotid Surgery Trialists' Collaborative Group 1998, Barnett et al. 1998, Ferguson et al. 1999, Rothwell et al. 1999, Rothwell et al. 2003, Rothwell et al. 2004). In both studies combined, an absolute risk reduction of 13.5% over 5 years was observed for the operation (carotid endarterectomy, CEA) compared to the conservative treatment of stenosis of >70% (Rothwell et al. 2004). In the subgroup of patients with a stenosis of >90% (without pseudo-occlusion) the absolute risk reduction was 32.6% after 3 years. This benefit is continuously observed after 5 and 8 years. In the group of patients with a stenosis of 50–69% the absolute risk reduction for the endpoint ipsilateral stroke was 4.6% after 5 years and 8% after 8 years (including all perioperative complications). In this group especially male patients showed a benefit (ARR 8% per 5 years); the benefit is highest if the operation is performed within 2 weeks. Patients with a carotid stenosis of <50% do not benefit from an operation. The perioperative complication rates were 6.2% (stenosis >70%) and 8.4% (stenosis 50–69%). In general, surgery looses its benefits if complication rates of the surgeon exceed 6%. Results reported by the operative departments are best traceable if for every patient an examination by a neurological specialist before and after the procedure is documented. Referring doctors and patients should be aware of the complication rates of a surgical or interventional center.

In 2006 two large randomised studies comparing stent-supported angioplasty (CAS) and operative therapy (CEA) were published. In both studies patients with a high-grade symptomatic carotid stenosis (amaurosis fugax, TIA, stroke) were included, who, in principal, were suitable for both treatments. In both studies it was requested prior to the beginning of the study that the treating physician (operation/stenting) was specifically qualified. Both SPACE and EVA3S had a non-inferiority-design. The use of a protection device was optional in SPACE. In EVA3S, the protocol was changed and a protection device was made mandatory after inclusion of 15 patients.

In the SPACE study, 1,200 symptomatic patients with a carotid stenosis (>50% according to NASCET or >70% according to ECST) were randomised within 6 months of the qualifying event (Ringleb et al. 2006). In the intention-to-treat-analysis the primary endpoint (ipsilateral stroke or death within 30 days) was observed 41 times in the CAS-group (6.84%) and 37 times in the CEA-group (6.34%). The absolute deviation was 0.51% (confidence interval of 95%; −2.37 to +3.39). As a non-inferiority-threshold was predefined at 2.5%, SPACE could not demonstrate a non-inferiority of CAS compared to CEA (p=0.09). For the two treatment regimens there was neither a statistical difference regarding the primary nor one of the secondary endpoints (disabling ipsilateral stroke, any stroke, technical failure), though for each endpoint a slight trend in favour of the operation was found. Similar results were found for the per-protocol-analysis. A subgroup-analysis of patients <68 years showed a lower periprocedural risk during CAS (2.7% vs. 7.0%) while patients ≥68 years had a lower risk for CEA (10.8% vs. 5.9%). This is due to age-dependency of the periprocedural risk in the CAS-group that was not observed in the CEA-group (Stingele et al. 2008).

In EVA3S, 527 patients with symptomatic carotid stenosis within the last 4 months and a stenosis of more than 60% according to ultrasound criteria were randomised (Mas et al. 2006). Due to an increased periprocedural complication rate (endpoint either stroke or death within 30 days) in the CAS-group (9.6% vs. 3.9%; OR 2.5; 95% CI 1.25–4.93) the study had to be stopped early. When the data of these two trials are combined with findings of earlier studies, a slight advantage for the operative treatment is found regarding the periprocedural risk (Kern et al. 2007). The long-term results of both methods are comparable. However, the number of restenoses is higher after stenting.

Secondary prevention in intracranial stenosis

Recommendations

- In patients with a high-grade intracranial stenosis or occlusion, a secondary prevention with antiplatelet drugs is recommended (B). Given the poor tolerance of the evidence based dose of 1300 mg of ASA, we recommend a prophylaxis with 100–300 mg (C).
- In recurrent events, a stent implantation in a centre with adequate neuroradiologic experience can be considered (C). After the procedure treatment with clopidogrel (75 mg) and ASA (100 mg) for a period of 1–3 months is recommended (C).

In the WASID-II study, 569 patients with an intracranial stenosis were included and treated with either 1300 mg of ASA or oral anticoagulation (INR 2–3). The study had to be stopped because of the elevated bleeding rate in the warfarin-therapy arm (Chimowitz et al. 2005). Therefore, prophylaxis with ASA is recommended. Because 1300 mg of ASA often is not tolerated, we rather recommend a lower dose. Predictors for a recurrent ischemic event were the grade of stenosis, a stenosis in the vertebrobasilar region and female gender (Kasner et al. 2006). Against expectations it did not help to keep the blood pressure > 140 / 90 mm Hg. If recurrent ischemic events occur during the intake of ASA, a stent implantation in a centre with adequate neuroradiological experience can be considered.

Secondary prevention in patent foramen ovale (PFO)

Recommendations

- In patients with PFO alone, regardless the size, and a first cerebral ischemic event, a prophylaxis with ASA (100 mg / d) is recommended (B).
- If a recurrent stroke occurs while taking ASA or if a PFO is combined with an atrial septum aneurysm oral anticoagulation with an INR of 2.0–3.0 for at least 2 years is recommended (C).
- If another recurrent stroke occurs or if there are contraindications against oral anticoagulation, interventional PFO closure can be considered (C).

Individuals with a patent foramen ovale have an increased risk for cryptogenic stroke, regardless of their age (Handke et al. 2007). Especially in younger stroke patients the occlusion of a PFO is discussed. As yet, there is little evidence that occlusion devices reduce the stroke rate in PFO patients. A big European multi-centre study showed a very low recurrent stroke risk during secondary prophylaxis with ASA (325 mg / d) which does not justify operation or placement of a PFO closure device (Mas et al. 2001). A practical recommendation of the American Academy of Neurology as well as a recommendation of the FDA declares that PFO is not associated with an elevated risk for death or second stroke (Messe et al. 2004, Slottow et al. 2007). Patients with an additional atrial septum aneurysm may have an elevated stroke risk. The European multi-centre study evaluating the recurrent stroke rate during ASA intake (325 mg / d) showed a low recurrent stroke rate of 0.6 % in PFO patients without atrial septum aneurysm (Mas et al. 2001) and a risk of 6 % per year in PFO with atrial septum aneurysm. However, very wide confidence intervals were reported. We recommend ASA doses of 100–300 mg / d for secondary prevention in stroke patients with PFO.

In the PICSS-study no difference was found regarding recurrent stroke between anticoagulation with warfarin and 325 mg ASA daily (Homma et al. 2002).

In many cardiological centres the implantation of PFO closure devices in patients with a cryptogenic stroke is propagated. This technical elegant form of mechanical PFO closure has to be seen critically not only because of the low recurrent stroke rate when taking ASA, but also because of a surprisingly high recurrent stroke rate of 3.4 % per year after the procedure. (Windecker et al. 2000). A review of 16 studies showed a risk for complications due to implantation of a closure device of 1.5–7.9 % with an annual recurrent stroke rate of 0–4.9 % while the 1-year recurrent stroke risk during non-invasive treatment was 3.8–12 % (Khairy et al. 2003). The comparison is complicated by the fact that in this review a TIA, minor and major stroke was globally counted as recurrent stroke, while the complications were separated in severe (death, severe bleeding, cardiosurgical revision and pulmonary embolism – 1.5 %) and moderate (arrhythmia, breaking of the device, device embolism, device thrombosis, and air embolisation – 7.9 %) complications. However, also the moderate complications seem to be threatening. An Italian publication reports a low recurrent stroke rate after device-closure but a persisting right-to-left shunt of 22 % and 9 % after 1 month and 12 months, respectively. They report atrial fibrillation in 8 % and a nickel-toxicity in 6 % (Anzola et al. 2004). Several multi-centre studies (RESPECT USA, PC-Trial Europe, CLOSURE USA) are designed to compare the device closure to the conservative treatment. Only after their availability a therapy recommendation can be given.

Specifics for Austria

Due to Austrian specifics in the health care sector and guidelines of the social insurance institutions, certain appraisals and recommendations differ slightly from the DGN-guidelines. In Austria, for years the recommendations for stroke diagnostics and treatment have been developed by the Austrian Society for Stroke Research (ÖGSF). For the special Austrian appraisals we would like to refer to the positioning paper of the ÖGSF from 2007.

Specifics for Switzerland

There are no restrictions for the use of these guidelines in Switzerland. A positioning paper by the „cerebrovascular workgroup of Switzerland“, edited by the topic-group „secondary prevention“ is in preparation. It is not expected that this paper will differ essentially from the DGN-guidelines.

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The guideline from 2005 was extensively discussed with physicians in clinical as well as private practice and requests for modifications and corrections have been included in this guideline. The current guideline was developed in the modified Delphi-method.

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Literature

1 *Abbott RD, Rodriguez BL, Burchfiel CM et al.* Physical activity in older middle-aged men and reduced risk of stroke: the Honolulu Heart Program. Am J Epidemiol 1994; 139: 881–893
2 *Abou-Chebl A, Yadav JS, Reginelli JP et al.* Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. J Am Coll Cardiol 2004; 43: 1596–1601
3 *Adams HP Jr, Effron MB, Torner J et al.* Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). Stroke 2008; 39: 87–99
4 *Akins PT, Feldman HA, Zoble RG et al.* Secondary stroke prevention with ximelagatran versus warfarin in patients with atrial fibrillation: pooled analysis of SPORTIF III and V clinical trials. Stroke 2007; 38: 874–880
5 *Algra A, de Schryver E, van Gijn J et al.* Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin. Cochrane Database Syst Rev 2006; 3: CD 001342
6 *Algra A, van Gijn J.* Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of arterial origin. J Neurol Neurosurg Psychiatry 1999; 65: 255
7 *Amarenco P, Goldstein LB, Szarek M et al.* Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 2007; 38: 3198–3204
8 *Amarenco P, Labreuche J, Lavallee P et al.* Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke 2004; 35: 2902–2909
9 *Anderson G, Limacher M, Assaf A et al.* Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. J Am Med Ass 2004; 291: 1701–1712
10 *Ansell J, Hirsh J, Dalen J et al.* Managing oral anticoagulant therapy. Chest 2001; 119 (Suppl 1): 22S–38S
11 *Antiplatelet Trialists' Collaboration.* Collaborative overview of randomised trials of antiplatelet therapy – I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J 1994; 308: 81–106
12 *Antithrombotic Trialists' Collaboration.* Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Br Med J 2002; 524: 71–86
13 *Anzola G, Morandi E, Casilli F et al.* Does transcatheter closure of patent foramen ovale really „shut the door?" – a prospective study with transcranial doppler. Stroke 2004; 35: 2140–2144
14 *Barnett HJ, Taylor DW, Eliasziw M et al.* Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med 1998; 339: 1415–1425
15 *Bejot Y, Benatru I, Rouaud O et al.* Epidemiology of stroke in Europe: geographic and environmental differences. J Neurol Sci 2007; 262: 85–88
16 *Beletsky V, Nadareishvili Z, Lynch J et al.* Cervical arterial dissection. Time for a therapeutic trial? Stroke 2003; 34: 2856–2860
17 *Bhatt DL, Flather MD, Hacke W et al.* Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 2007; 49: 1982–1988
18 *Blanco M, Nombela F, Castellanos M et al.* Statin treatment withdrawal in ischemic stroke: a controlled randomized study. Neurology 2007; 69: 904–910
19 *Bonaa KH, Njolstad I, Ueland PM et al.* Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006; 354: 1578–1588
20 *Bond R, Rerkasem K, Rothwell PM.* Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. Stroke 2003; 34: 2290–2303
21 *Bond R, Rerkasem K, Shearman CP et al.* Time trends in the published risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. Cerebrovasc Dis 2004; 18: 37–46
22 *Born G, Patrono C.* Antiplatelet drugs. Br J Pharmacol 2006; 147 (Suppl 1): S 241–S 251
23 *Burry K.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. Curr Womens Health Rep 2002; 2: 331–332
24 *Burton A.* Abciximab extends treatment window for stroke. Lancet Neurology 2003; 2: 390
25 *Cannegieter S, Rosendaal F, Wintzen A et al.* Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995; 333: 11–17
26 *Cannon CP, Braunwald E, McCabe CH et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495–1504
27 *CAPRIE Steering Committee.* A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348: 1329–1339
28 *Chan F, Ching J, Hung L et al.* Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005; 352: 238–244
29 *Chimowitz MI, Lynn MJ, Howlett-Smith H et al.* Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005; 352: 1305–1316
30 *Cholesterol Treatment Trialists' (CTT) Collaborators.* Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371: 117–125
31 *Christensen R, Kristensen PK, Bartels EM et al.* Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet 2007; 370: 1706–1713
32 *Colhoun HM, Betteridge DJ, Durrington PN et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Col-

laborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364: 685–696
33 *Collaborative Group of the Primary Prevention Project (PPP).* Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Lancet 2001; 357: 89–95
34 *Collins R, Armitage J, Parish S et al.* Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004; 363: 757–767
35 *Collins R, Peto R, MacMahon S et al.* Blood pressure, stroke and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. Lancet 1990; 335: 827–838
36 *Connolly S, Pogue J, Hart R et al.* Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006; 367: 1903–1912
37 *Curioni C, Andre C, Veras R.* Weight reduction for primary prevention of stroke in adults with overweight or obesity. Cochrane Database Syst Rev 2006; (4): CD 006062
38 *Dahlof B, Devereux RB, Kjeldsen SE et al.* Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359: 995–1003
39 *Dahlof B, Sever PS, Poulter NR et al.* Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005; 366: 895–906
40 *de Lemos JA, Blazing MA, Wiviott SD et al.* Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. J Am Med Ass 2004; 292: 1307–1316
41 *Diener HC.* Modified-release dipyridamole combined with aspirin for secondary stroke prevention. Aging Health 2005; 1: 19–26
42 *Diener H, Bogousslavsky J, Brass L et al.* Acetylsalicylic acid on a background of clopidogrel in high-risk patients randomised after recent ischaemic stroke or transient ischaemic attack: The MATCH trial results. Lancet 2004a; 364: 331–334
43 *Diener HC, Cuhna L, Forbes C et al.* European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143: 1–13
44 *Diener HC, Darius H, Bertrand-Hardy JM et al.* Cardiac safety in the European stroke prevention study 2 (ESPS 2). Int J Clin Pract 2001; 55: 162–163
45 *Diener HC, Ringleb PA, Savi P.* Clopidogrel for secondary prevention of stroke. Expert Opin Pharmacother 2005; 6: 755–764
46 *Diener HC, Sacco R, Yusuf S et al.* Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens and telmisartan versus placebo in patients with strokes: the prevention regimen for effectively avoiding second strokes (PRoFESS) trial. Cerebrovasc Dis 2007; 23: 368–380
47 *Diener H, Welch K, Mohr J.* Migraine and stroke. In: Mohr J, Choi D, Grotta J, Weir B, Wolf PA, eds. Stroke. Pathophysiology, diagnosis and management. Philadelphia: Churchill Livingstone, 2004b: 629–640
48 *Droste D, Ritter M, Dittrich R et al.* Arterial hypertension and ischaemic stroke. Acta Neurol Scand 2003; 107: 241–251
49 *EAFT Group.* Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993; 342: 1255–1262
50 *Endres M.* Statins and stroke. J Cereb Blood Flow Metab 2005; 25: 1093–1110
51 *Endres M, Laufs U.* Discontinuation of statin treatment in stroke patients. Stroke 2006; 37: 2640–2643
52 *European Carotid Surgery Trialists' Collaborative Group.* MRC European carotid surgery trial: interim results for symptomatic patients with severe carotid stenosis and with mild carotid stenosis. Lancet 1991; 337: 1235–1243
53 *European Carotid Surgery Trialists' Collaborative Group.* Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351: 1379–1387
54 *Executive Committee for the Asymptomatic Carotid Atherosclerosis Study.* Endarterectomy for asymptomatic carotid artery stenosis. J Am Med Ass 1995; 273: 1421–1428
55 *Ferguson GG, Eliasziw M, Barr HWK et al.* The North American symptomatic carotid endarterectomy trial: surgical result in 1415 patients. Stroke 1999; 30: 1751–1758
56 *Fiebach JB, Schellinger PD, Jansen O et al.* CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. Stroke 2002; 33: 2206–2210
57 *Flather MD, Yusuf S, Kober L et al.* Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000; 355: 1575–1581
58 *Fuster V, Ryden LE, Cannom DS et al.* ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation [full text: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society]. Europace 2006; 8: 651–745
59 *Gaede P, Vedel P, Larsen N et al.* Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383–393
60 *Gage BF, Waterman AD, Shannon W et al.* Validation of clinical classification schemes for predicting stroke results from the national registry of atrial fibrillation. J Am Med Ass 2001; 285: 2864–2870
61 *Giles MF, Rothwell PM.* Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2007; 6: 1063–1072
62 *Gilon D, Bounanno FS, Joffe MM et al.* Lack of evidence of an association between mitral-valve prolapse and stroke in young patients. N Engl J Med 1999; 341: 8–13
63 *Goldstein LB, Adams R, Becker KJ et al.* Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2001; 32: 280–299
64 *Goldstein LB, Amarenco P, Szarek M et al.* Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology 2007; 68: 737–742
65 *Gonzales D, Rennard SI, Nides M et al.* Varenicline, an alpha-4 beta-2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. J Am Med Ass 2006; 296: 47–55
66 *Grady D, Herrington D, Bittner V et al.* Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). J Am Med Ass 2002; 288: 99–101
67 *Grau AJ, Weimar C, Buggle F et al.* Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. Stroke 2001; 32: 2559–2566
68 *Grundy SM, Cleeman JI, Merz CN et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol 2004; 44: 720–732
69 *Hacke W, Donnan G, Fieschi C et al.* Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004; 363: 768–774
70 *Halliday A, Mansfield A, Marro J et al.* Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004; 363: 1491–1502
71 *Handke M, Harloff A, Olschewski M et al.* Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 2007; 357: 2262–2268
72 *Hansson L, Lindholm LH, Ekbom T et al.* Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in old patients with hypertension-2 study. Lancet 1999; 354: 1751–1756
73 *Hardman SMC, Cowie MR.* Anticoagulation in heart disease. Br Med J 1999; 318: 238–244
74 *Hart R, Benavente O, McBride R et al.* Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999; 131: 492–501
75 *Hart R, Pearce L, Miller V et al.* Cardioembolic versus noncardioembolic strokes in atrial fibrillation: Frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. Cerebrovasc Dis 2000a; 10: 39–43
76 *Hart RG, Halperin JL.* Atrial fibrillation and stroke: concepts and controversies. Stroke 2001; 32: 803–808

77 *Hart RG, Halperin JL, McBride R et al.* Aspirin for the primary prevention of stroke and other major vascular events. Meta-analysis and hypotheses. Arch Neurol 2000b; 57: 326–332
78 *Heart Protection Study Collaborative Group.* MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7–22
79 *Heuschmann PU, Heidrich J, Wellmann J et al.* Stroke mortality and morbidity attributable to passive smoking in Germany. Eur J Cardiovasc Prev Rehabil 2007; 14: 793–795
80 *Hill MD, Yiannakoulias N, Jeerakathil T et al.* The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004; 62: 2015–2020
81 *Homma S, Sacco RL, Di Tullio MR et al.* Effect of medical treatment in stroke patients with patent foramen ovale. Circulation 2002; 105: 2625–2631
82 *Hughes JR, Stead LF, Lancaster T.* Antidepressants for smoking cessation. Cochrane Database Syst Rev 2007; (1): CD 000031
83 *Hylek EM, Evans-Molina C, Shea C et al.* Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007; 115: 2689–2696
84 *International Society of Hypertension Writing Group.* International Society of Hypertension (ISH): Statement on the Management of Blood Pressure in Acute Stroke. Journal of Hypertension 2003; 21: 665–672
85 *Iso H, Date C, Yamamoto A et al.* Smoking cessation and mortality from cardiovascular disease among Japanese men and women: the JACC Study. Am J Epidemiol 2005; 161: 170–179
86 *Iso H, Hennekens CH, Stampfer MJ et al.* Prospective study of aspirin use and risk of stroke in women. Stroke 1999; 30: 1764–1771
87 *Iso H, Jacobs DR, Wentworth D et al.* Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N Engl J Med 1989; 320: 904–910
88 *Johnston SC, Gress DR, Browner WS et al.* Short-term prognosis after emergency department diagnosis of TIA. J Am Med Ass 2000; 284: 2901–2906
89 *Jorenby DE, Hays JT, Rigotti NA et al.* Efficacy of varenicline, an alpha4-beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. J Am Med Ass 2006; 296: 56–63
90 *Junghans U, Seitz RJ, Aulich A et al.* Bleeding risk of tirofiban, a non-peptide GPIIb/IIIa platelet receptor antagonist in progressive stroke: An open pilot study. Cerebrovasc Dis 2001; 12: 308–312
91 *Kasner SE, Chimowitz MI, Lynn MJ et al.* Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation 2006; 113: 555–563
92 *Kawachi I, Colditz GA, Stampfer MJ et al.* Smoking cessation and decreased risk of stroke in women. J Am Med Ass 1993; 269: 232–236
93 *Keil U, Becher H, Heidrich J et al.* Passivrauchbedingte Morbidität und Mortalität in Deutschland. In: Deutsches Krebsforschungszentrum Heidelberg, Hrsg. Passivrauchen – ein unterschätztes Gesundheitsrisiko. Heidelberg: 2006: 20–59
94 *Kern R, Ringleb PA, Hacke W et al.* Stenting for carotid artery stenosis. Nat Clin Pract Neurol 2007; 3: 212–220
95 *Khairy P, O'Donnell CP, Landzberg MJ.* Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. Ann Intern Med 2003; 139: 753–760
96 *Khaw KT.* Epidemiology of stroke. J Neurol Neurosurg Psychiatry 1996; 61: 333–338
97 *Kiely DK, Wolf PA, Cupples LA et al.* Physical activity and stroke risk: the Framingham Study. Am J Epidemiol 1994; 140: 608–620
98 *Kurth T, Gaziano JM, Berger K et al.* Body mass index and the risk of stroke in men. Arch Intern Med 2002; 162: 2557–2562
99 *Lam TH, Li ZB, Ho SY et al.* Smoking, quitting and mortality in an elderly cohort of 56,000 Hong Kong Chinese. Tob Control 2007; 16: 182–189
100 *LaRosa JC, Grundy SM, Waters DD et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352: 1425–1435
101 *Lee C, Folsom A, Blair S.* Physical activity and stroke risk: A meta-analysis. Stroke 2003; 34: 2475–2481
102 *Lee IM, Hennekens CH, Berger K et al.* Exercise and risk of stroke in male physicians. Stroke 1999; 30: 1–6
103 *Leppala JM, Virtamo J, Fogelholm R et al.* Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. Stroke 1999; 30: 2535–2540
104 *Lewington S, Whitlock G, Clarke R et al.* Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007; 370: 1829–1839
105 *Lindholm LH, Carlberg B, Samuelsson O.* Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet 2005; 366: 1545–1553
106 *Lindholm LH, Ibsen H, Dahlof B et al.* Cardiovascular morbidity and mortality in patients with diabetes in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359: 1004–1010
107 *Lovett J, Coull A, Rothwell P.* Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 2004; 62: 569–573
108 *Lyrer P, Engelter S.* Antithrombotic drugs for carotid artery dissection. Stroke 2004; 35: 613–614
109 *Mant J, Hobbs F, Fletcher K et al.* Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007; 370: 493–503
110 *Mas JL, Arquizan C, Lamy C et al.* Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001; 345: 1740–1746
111 *Mas JL et al, for the EVA-3S Investigators.* Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006; 355: 1660–1671
112 *Merikangas KR, Fenton BT, Cheng SH et al.* Association between migraine and stroke in a large-scale epidemiological study of the United States. Arch Neurol 1997; 54: 362–368
113 *Messe S, Silverman I, Kizer J et al.* Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004; 62: 1042–1050
114 *Mohr JP, Thompson JL, Lazar RM et al.* A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001; 345: 1444–1451
115 *Moore WS, Vescera CL, Robertson JT et al.* Selection process for surgeons in the asymptomatic carotid atherosclerosis study. Stroke 1991; 22: 1353–1357
116 *Neter JE, Stam BE, Kok FJ et al.* Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension 2003; 42: 878–884
117 *Nieuwlaat R, Capucci A, Camm AJ et al.* Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005; 26: 2422–2434
118 *Overell JR, Bone I, Less KR.* Interatrial septal abnormalities and stroke. A meta-analysis of case-control studies. Neurology 2000; 55: 1172–1179
119 *Paciaroni M, Hennerici M, Agnelli G et al.* Statins and stroke prevention. Cerebrovasc Dis 2007; 24: 170–182
120 *Patrono C, Garcia RodriguezLA, Landolfi R et al.* Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005; 353: 2373–2383
121 *Peto R, Gray R, Collins R et al.* Randomised trial of prophylactic daily aspirin in British male doctors. Brit Med J 1988; 296: 313–316
122 *Pi-Sunyer FX, Aronne LJ, Heshmati HM et al.* Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. J Am Med Ass 2006; 295: 761–775
123 *Progress Collaborative Group.* Randomised trial of a perindopril-based blood-pressure lowering regimen among individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358: 1033–1041
124 *Rashid P, Leonardi-Bee J, Bath P.* Blood pressure reduction and secondary prevention of stroke and other vascular events. A systematic review. Stroke 2003; 34: 2741–2749
125 *Ridker PM, Cook NR, Lee IM et al.* A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005; 352: 1293–1304
126 *Ringleb PA, Allenberg J, Bruckmann H et al.* 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006; 368: 1239–1247
127 *Rothwell P, Eliasziw M, Gutnikov S et al.* Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004; 363: 915–924

128 *Rothwell PM, Eliasziv M, Gutnikov SA et al.* Analysis of pooled data from the randomized controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003; 361: 107–116
129 *Rothwell PM, Warlow CP on behalf of the European Carotid Surgery Trialists' Collaborative Group.* Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. Lancet 1999; 353: 2105–2110
130 *Sacks FM, Svetkey LP, Vollmer WM et al.* Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. N Engl J Med 2001; 344: 3–10
131 *Salem DN, Levine HJ, Pauker SG et al.* Antithrombotic therapy in valvular heart disease. Chest 1998; 114 (Suppl): 590S–601S
132 *Saxena R, Koudstaal PJ.* Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack. Stroke 2004; 35: 1782–1783
133 *Scheen AJ, Finer N, Hollander P et al.* Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006; 368: 1660–1672
134 *Schrader J, Lüders S, Kulschewski A et al.* The ACCESS Study: evaluation of acute candesartan cilexetil therapy in stroke survivors. Stroke 2003; 34: 1699–1703
135 *Schrader J, Lüders S, Kulschewski A et al.* Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). Stroke 2005; 36: 1218–1226
136 *Seitz R, Hamzavi M, Junghans U et al.* Thrombolysis with recombinant tissue plasminogen activator and tirofiban in stroke: preliminary observations. Stroke 2003; 34: 1932–1935
137 *Sever P, Dahlof B, Poulter N et al.* Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361: 1149–1158
138 *Shahar E, Chambless L, Rosamond W et al.* Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2003; 34: 623–631
139 *Shepherd J, Blauw GJ, Murphy MB et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360: 1623–1630
140 *Shinton R, Beevers G.* Meta-analysis of relation between cigarette smoking and stroke. Br Med J 1989; 298: 789–794
141 *Singer DE, Albers GW, Dalen JE et al.* Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126 (Suppl 3): 429S–456S
142 *Slottow TL, Steinberg DH, Waksman R.* Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel meeting on patent foramen ovale closure devices. Circulation 2007; 116: 677–682
143 *Staessen JA, Gasowski J, Wang JG et al.* Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000; 355: 865–872
144 *Staessen JA, Wang JG, Thijs L.* Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305–1315
145 *Stingele R, Berger J, Alfke K et al.* Clinical and angiographic risk factors for stroke and death within 30 days after carotid endarterectomy and stent-protected angioplasty: a subanalysis of the SPACE study. Lancet Neurology 2008; 7: 216–222
146 *Stratton IM, Adler AI, Neil HAW et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Br J Med 2000; 321: 405–412
147 *The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group.* Major cardiovascular events in hypertensive patients randomized to doxazosin versus chlorthalidone. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Am Med Ass 2000; 283: 1967–1975
148 *The ESPRIT Study Group.* Aspirin plus Dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006; 367: 1665–1673
149 *The ESPRIT Study Group.* Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurology 2007; 6: 115–124
150 *The ESPS Group.* The European Stroke Prevention Study (ESPS). Principal end-points. Lancet 1987; ii: 1351–1354
151 *The Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators.* Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006; 354: 1567–1577
152 *The Steering Committee of the Physicians' Health Study Research Group.* Aspirin for the primary prevention of myocardial infarction. N Engl J Med 1988; 318: 245–264
153 *The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators.* High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006; 355: 549–559
154 *The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group.* A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. Ann Neurol 1997; 42: 857–865
155 *Toole JF, Malinow MR, Chambless LE et al.* Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. J Am Med Ass 2004; 291: 565–575
156 *Topol E, Easton D, Harrington R et al.* Randomized, double-blind, placebo-controlled, international trial of the oral IIb/IIIa antagonist lotrafiban in coronary and cerebrovascular disease. Circulation 2003; 108: 16–23
157 *Topol EJ, Byzova TV, Plow EF.* Platelet GPIIb-IIIa blockers. Lancet 1999; 353: 227–231
158 *Turner R, Cull C, Frighi V et al.* Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. J Am Med Ass 1999; 281: 2005–2012
159 *UK Prospective Diabetes Study (UKPDS) Group.* Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352: 837–853
160 *Viscoli CM, Brass LM, Kernan WN et al.* A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med 2001; 345: 1243–1249
161 *Wannamethee SG, Shaper AG, Ebrahim S.* HDL-Cholesterol, total cholesterol and the risk of stroke in middle-aged British men. Stroke 2000; 31: 1882–1888
162 *Wannamethee SG, Shaper AG, Whincup PH et al.* Smoking cessation and the risk of stroke in middle-aged men. J Am Med Ass 1995; 274: 155–160
163 *Waters DD, Schwartz GG, Olsson AG et al.* Effects of atorvastatin on stroke in patients with unstable angina or non-Q-wave myocardial infarction: a Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) substudy. Circulation 2002; 106: 1690–1695
164 *Weimar C, Goertler M, Rother J et al.* Systemic Risk Score Evaluation in Ischemic Stroke Patients (SCALA): A prospective cross sectional study in 85 German stroke units. J Neurol 2007; 254: 1562–1568
165 *Weimar C, Roth MP, Zillessen G et al.* Complications following acute ischemic stroke. Eur Neurol 2002; 48: 133–140
166 *Wilcox R, Bousser MG, Betteridge DJ et al.* Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke 2007; 38: 865–873
167 *Wilson PW, Garrison RJ, Castelli WP.* Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham Study. N Engl J Med 1985; 313: 1038–1043
168 *Wilson PWF, Hoeg JM, D'Agostino RB et al.* Cumultative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. N Engl J Med 1997; 337: 516–522
169 *Windecker S, Wahl A, Chatterjee T et al.* Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. Circulation 2000; 101: 893–898
170 *Wolf PA, Cobb JL, D'Agostino RB.* Epidemiology of stroke. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, eds. Stroke: pathophysiology, diagnosis and management. New York: Churchill Livingston, 1992: 3–27
171 *Yadav JS, Wholey MH, Kuntz RE et al.* Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004; 351: 1493–1501
172 *Yusuf S, Zhao F, Mehta SR et al.* Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494–502