

European Stroke Initiative  
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# Ischaemic Stroke

**Prophylaxis and Treatment**  
**Information for doctors in hospitals and practice**

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## I Introduction

Acute stroke is one of the leading factors of morbidity and mortality worldwide. Until recently, the acute care of stroke patients was characterized by therapeutic nihilism. However, increasing pathophysiologic knowledge and novel therapies for acute stroke has changed the management of stroke patients. Acute stroke is increasingly recognized as a medical emergency. Acute stroke management in specialized wards (stroke units) has been proven to be effective in acute ischaemic stroke. Although not available everywhere, thrombolytic therapy offers an additional treatment option.

In this folder, we give an updated clinical overview of ischaemic stroke with special emphasis on therapy and prevention following the recommendations proposed by the

### *European Stroke Initiative*

Used levels of evidence (LoE):

**Level I:** Highest Level of Evidence. Primary endpoint of RCT with adequate sample size or Meta-analysis of qualitatively outstanding RCTs

**Level II:** Intermediate Level of Evidence. Small randomised trials or predefined secondary endpoints of large RCTs

**Level III:** Lower Level of Evidence. Prospective case series with concurrent or historical control or post hoc analyses of large RCTs

**Level IV:** Undetermined Level of Evidence. Small uncontrolled case series of general agreement despite lack of evidence

## Definition

Stroke is defined as a sudden neurologic deficit due to central nervous ischaemia or haemorrhage. We concentrate here on ischaemic stroke, which accounts for about 75% of all strokes. Ischaemic stroke is caused by focal vessel occlusion leading to cessation of oxygen and glucose supply to the brain with subsequent breakdown of the metabolic processes in the affected territory.

## Epidemiology

Stroke is, after cardiovascular disease and cancer, the third most common cause of death in industrialized countries. In Europe yearly mortality rates from 63.5 to 273.4/100.000. Stroke is the most important cause of morbidity and long term disability in Europe as well as in other industrialized nations. The incidence of stroke varies in different European countries. It is estimated to be between 100 and 200 new strokes / 100.000 inhabitants / year. This imposes an enormous economic burden.

## II Pathophysiology and Etiology

### Pathophysiology of Ischaemic Stroke

After cessation of blood supply following occlusion or hypoperfusion of a cerebral vessel, neuronal cell death occurs in the core of the infarcted area within few minutes. The area surrounding the core, called the ischaemic *penumbra*, contains functionally impaired but still viable brain tissue supplied with blood from collateral vessels. This area may be transformed into infarction due to secondary neuronal damage induced by deleterious biochemical cascades resulting in cytotoxic and excitotoxic effects.

### Stroke Etiology

While biochemical processes of ischaemic brain damage are uniform, there are a number of different causes of stroke, which include:

- atherosclerotic and atherothrombotic stenotic lesions of extracranial cervical and large basal cerebral arteries leading to critical hypoperfusion distally to high-grade stenoses
- arterio-arterial emboli from atherothrombotic lesions leading to intracranial vessel occlusion
- systemic embolism (cardiac sources such as prosthetic valves, atrial fibrillation, cardiac

thrombi, dilated cardiomyopathy, recent myocardial infarction, or intracardiac shunts)

- lipohyalinosis of small vessels, leading to microangiopathic lacunar lesions

Less common causes include cervical artery dissection, vasculitis, or thrombosis due to coagulopathies.

## III Signs and Symptoms

Symptoms and signs vary with the brain territory involved. However, certain symptoms are frequently found. They include:

- contralateral weakness and/or sensory loss
- aphasia, apraxia, dysarthria
- partial or complete hemianopsia
- disturbances of consciousness and confusion
- diplopia, vertigo, nystagmus, ataxia

## IV Acute Management of Ischaemic Stroke

There are six mainstays in the management of acute ischaemic stroke:

- Diagnostics to confirm diagnosis and provide the opportunity to make therapeutical decisions

- Treatment of general conditions that influence long-term functional outcome (blood pressure, body temperature, glucose level)
- Specific therapy directed against particular aspects of stroke pathogenesis, either recanalisation of a vessel occlusion or prevention of mechanisms leading to neuronal death (neuroprotection)
- Prophylaxis and treatment of complications, either medical (such as aspiration, infections, decubital ulcers, deep venous thrombosis, or pulmonary embolism) or neurological (such as secondary haemorrhage, space-occupying oedema or seizures)
- Early secondary prevention, to reduce the incidence of early stroke recurrence
- Early rehabilitation

### **Diagnostic Procedures**

Early identification of stroke such as ischaemia, intracerebral haemorrhage, or SAH is essential for the stroke management. Based on the physical and neurological evaluation, and skilled use and interpretation of emergent diagnostic tests, different causes of ischaemic stroke may be identified. This may influence the use of specific therapeutic

procedures and the correct choice of secondary prophylaxis.

### **Neuroimaging**

A *non-contrast cranial computed tomography (CT) scan* reliably distinguishes between ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage (SAH). It should be performed before initiation of specific treatment. Today, state-of-the-art devices allow the early effects of ischaemia to be recognized very early within the first 3-6 hours of onset (early signs: lowered X-ray absorption of gray matter, focal obliteration of sulci and cisterns, hyperdense MCA sign).

With *CT angiography* using spiral CT technique, the patency or occlusion of large intracranial arteries can be assessed quickly and safely.

Modern *magnetic resonance imaging (MRI)* sequences, such as diffusion- and perfusion-weighted imaging, are helpful to identify the quantity of the infarcted area and the amount of tissue at risk, even for smaller brain stem infarctions. T2\*-weighted imaging is even more sensitive than CT for the display of intracerebral haemorrhage. MR angiography can be used to identify obliterations in the major intracranial arteries. However, these techniques are not widely available yet.

## Electrocardiogram

An ECG is indispensable because of the high incidence of heart diseases in stroke patients. Atrial fibrillation or recent myocardial infarction may be seen as embolic sources, the latter prohibiting thrombolysis at the same time.

## Ultrasound

Doppler- and duplexsonography of extracranial and intracranial arteries allow to identify vessel occlusion or stenosis, state of collaterals, or recanalization.

Other ultrasound studies include transthoracic and transoesophageal echocardiography to screen for cardioembolic conditions. They usually are not performed in the ER, but it seems useful to have these studies available in the first 24 hours after stroke onset.

Peripheral arteries are frequently affected by atherothrombosis. The ankle-brachial-index (ABI) is an easy test for the assessment of asymptomatic peripheral artery disease. An ABI of  $< 0.9$  is an independent risk factor for cardiovascular and cerebrovascular disease.

## Laboratory Tests

They include haematology, clotting parameters, electrolytes, hepatic and renal chemistry, and basic markers of infection.

In case of normal CT findings and clinical suspicion of SAH, a lumbar puncture should be performed.

Useful laboratory parameters after stroke are:

### Routine tests

- Complete blood count and platelet count
- INR, PTT
- Serum electrolytes
- Blood glucose
- CRP, sedimentation rate
- Hepatic and renal chemical analyses

### Special laboratory tests (in selected patients)

- Protein C, S, aPC-resistance
- Cardiolipin-AB
- Homocystein
- Vasculitis-screening (ANA, Lupus AC)
- CSF

## General Stroke Treatment and Monitoring

Once the patient has arrived in the emergency department, he first has to be examined for potentially life-threatening complications, with emphasis on the airway, respiratory function and

circulation. The following parameters should be monitored and/or treated in the ER, stroke unit (see below) or normal ward:

### **Clinical**

Regular observation to recognize impaired pulmonary and circulatory function and to recognize complications from mass effects (vigilance, pupils) is recommended. The neurological status is best monitored using validated neurological scales, such as the NIH Stroke Scale, the Scandinavian Stroke Scale, the Glasgow Coma Scale and others.

### **Monitoring**

ECG monitoring is recommended because of the risk of malignant secondary or pre-existent arrhythmias and to detect atrial fibrillation as a source of embolism.

Continuous cardiac monitoring is recommended in the first 48 hours of stroke onset particularly in patients with:

- previous known cardiopathies
- history of arrhythmias
- unstable blood pressure
- clinical signs/symptoms of heart failure
- abnormal baseline ECG
- infarct involving the insular cortex

### **Cardiac Care**

Optimizing cardiac output with maintenance of a high normal BP and a normal heart rate is the essential basis of stroke management. The central venous pressure should be maintained at approximately 8–10 cm H<sub>2</sub>O, and its monitoring, although not frequently used in a normal ward, will give early warning of a volume deficiency or volume overload, which both have negative effects on cerebral perfusion.

Restoration of normal cardiac rhythm using drugs, cardioversion, or pacemaker should be performed in cooperation with internists or cardiologists, if necessary.

### **Blood Pressure**

Blood pressure is frequently elevated after ischaemic stroke. Blood pressure should be kept high in ischaemic infarctions to optimize perfusion of collaterals and stenosed vessels and to favor adequate flow in the critical penumbra, where CBF autoregulation is impaired. However, blood pressure should be lowered in haemorrhage or if cardiologic conditions require. Hypotension should be treated with fluids and/or norepinephrine.

## **Pulmonary Function**

Pulmonary and airway function or blood oxygenation should be monitored by pulse oximetry, if available. Especially patients with brainstem stroke and malignant MCA infarction are at risk for respiratory insufficiency due to hypoventilation, airway obstruction and aspiration. Adequate oxygenation may be important for the preservation of metabolic turnover in the penumbra. Oxygenation can be improved by administration of 2-4 l O<sub>2</sub>/min via nasal tube.

Intubation is recommended in case of potentially reversible respiratory insufficiency.

## **Glucose Metabolism**

Blood glucose should be monitored regularly, since preexisting diabetic metabolic derangement may be worsened in the acute phase of stroke, and hyperglycaemia may reduce functional outcome. Hypoglycaemia worsens outcome as well or can mimic cerebral infarction.

## **Fluid and Electrolytes**

Fluid and electrolyte status should be closely monitored and corrected to avoid plasma volume contraction, raised haematocrit, and impairment of rheologic properties of the blood. Hypotonic solutions (NaCl 0.45% or glucose 5%) are

contraindicated due to the risk of brain oedema increase consequent to reduction of plasma osmolality.

## **Body Temperature**

Fever negatively influences outcome after stroke and, experimentally, increases infarct size.

### *Recommendations (all LoE IV)*

- Continuous cardiac monitoring is recommended in the first 48 h of stroke onset particularly in patients with: previous known cardiac disease, history of arrhythmias, unstable blood pressure, clinical signs/symptoms of heart failure, abnormal baseline ECG and infarct involving the insular cortex
- Oxygenation monitoring with pulse oxymetry is recommended
- O<sub>2</sub>-administration is recommended in case of hypoxia (blood gas analysis or O<sub>2sat</sub><92% at pulse oxymetry)
- Intubation is recommended in case of potentially reversible respiratory insufficiency
- Routine bloodpressure lowering is not recommended, except for extremely elevated values (>200-220 mmHg systolic or 120 mmHg diastolic for ischaemic stroke, > 180/105 mmHg for haemorrhagic stroke) confirmed by repeated measurements
- Immediate antihypertensive therapy for more moderate hypertension is recommended in case of stroke and heart failure, aortic dissection, acute myocardial infarction, acute renal failure, thrombolysis or i.v. heparin.

- Recommended target blood pressure in patients with prior hypertension: 180/100-105 mmHg, without prior hypertension: 160-180/90-100 mmHg and under thrombolysis avoid systolic blood pressure above 180 mmHg
- Recommended drugs for BP treatment are i.v. Labetalol or Urapidil, i.v. Sodium Nitroprusside or Nitroglycerin and oral Captopril
- Avoid Nifedipine and any drastic BP decrease
- Avoid and treat hypotension particularly in unstable patients by administering adequate amounts of fluids and, when required, volume expanders and/or catecholamines (epinephrine 0.1-2 mg/h plus dobutamine 5-50 mg/h)
- Monitoring of serum glucose levels is recommended, particularly in known diabetic patients
- Glucose solutions are not recommended due to the detrimental effects of hyperglycaemia
- Treatment of serum glucose levels >10 mMol/L with insulin titration is recommended
- Immediate correction of hypoglycaemia is recommended by i.v. dextrose bolus or infusion of 10%-20% glucose
- Treatment of body temperature  $\geq 37.5^{\circ}\text{C}$  is recommended
- In case of fever the search of a possible infection (site and aetiology) is recommended, in order to start tailored antibiotic treatment
- Antibiotic, anti-mycotic or anti-viral prophylaxis is not recommended in immuno-competent patients
- Monitoring and correction of electrolyte and fluid disturbances are recommended

- Hypotonic solutions (NaCl 0.45% or glucose 5%) are contraindicated due to the risk of brain oedema increase consequent to reduction of plasma osmolality

## Specific Treatment

### a) Recanalizing Therapy

#### Thrombolysis

Administration of early thrombolytic therapy in ischaemic stroke is based on the concept that early restoration of circulation in the affected territory by recanalization of an occluded intracranial artery preserves reversibly damaged neuronal tissue in the penumbra. The recovery of neuronal function reduces clinical neurologic disability.

Based on a number of large multicenter studies, following *recommendations* can be derived for centers offering thrombolysis:

- Intravenous rtPA (0.9 mg/kg; maximum of 90 mg), with 10% of the dose given as a bolus, following by an infusion lasting 60 minutes is recommended within 3h of onset of ischaemic stroke (LoE I)
- The benefit from the use of i.v. rtPA for acute ischaemic stroke beyond 3 h after onset of the symptoms is smaller, but present up to 4.5 hours (LoE I)

- Intravenous rtPA is not recommended when the time of stroke onset cannot be ascertained reliably; this includes persons whose strokes are recognised upon awakening (LoE IV)
- Intravenous administration of streptokinase is dangerous and not indicated for the management of persons with ischaemic stroke (LoE I)
- Data on the efficacy and safety of any other intravenously administered thrombolytic drugs are not available to provide a recommendation
- Intraarterial treatment of acute middle cerebral artery occlusion in a 6-hour time window using pro-urokinase results in a significantly improved outcome (LoE II)
- Acute basilar occlusion may be treated with intraarterial therapy in selected centres in an institutional protocol as experimental therapy or within a multicenter clinical trial (LoE IV)

### Defibrinating Enzymes

Ancrod can presently not be recommended for use in acute ischaemic stroke outside the setting of clinical trials.

### b) Antithrombotic Therapy

#### Platelet Inhibitors

Large, randomized studies (IST,CAST) indicate that ASA (100-300 mg) given within 48 hours after stroke reduces mortality and rate of recurrent stroke minimally but significantly.

#### *Recommendations*

- Aspirin (100-300mg per day) may be given within 48h after ischaemic stroke (LoE I)
- If thrombolytic therapy is planned, no Aspirin should be given
- Aspirin is not allowed for 24 hours after thrombolytic therapy

#### Heparines and Heparinoids

Early anticoagulation with full-dose heparin or heparinoids in equivalent doses cannot be recommended for general use. Trends towards improvement in outcome or recurrency rates seem to be counterbalanced by an increased risk of haemorrhagic complications.

Full-dose heparin treatment after stroke currently may be proposed for a few indications if contra-indications such as haemorrhage or large infarction (e.g. more than 50% of the MCA territory) are excluded.

#### *Recommendations*

- There is no recommendation for general use of heparin, low-molecular weight heparin or heparinoids after ischaemic stroke (LoE I)
- Full-dose heparin may be used when there are selected indications such as cardiac sourced with high risk of rechts-embolism, arterial dissection, or high grade arterial stenosis prior to surgery (LoE IV)

Administration of low-dose heparin or low molecular weight heparin in an equivalent dose is always recommended in bedridden patients to reduce the number of deep venous thrombosis and pulmonary embolism (LoE II).

### **c) Haemodilution**

The clinical benefit of haemodilution therapy has not been established, and the possibility of excess brain oedema has not been excluded. This therapy is not presently recommended for the management of patients with acute ischaemic stroke (LoE I).

### **d) Neuroprotectants**

Currently, there is no recommendation to treat stroke patients with one of these agents (LoE I).

### **Stroke Units**

There is clear evidence that treatment of patients with ischaemic stroke on stroke units significantly reduces mortality, handicap and need for institutional care compared to treatment on a general medical ward.

A stroke unit is a hospital unit or part of a hospital that exclusively or nearly exclusively takes care of stroke patients. Stroke units are characterized by a specially trained staff and the multidisciplinary approach to treatment and care. The core disciplines of the stroke team are: Medical (neurologic and intern/cardiologic), nursing, physiotherapy,

occupational therapy, speech and language therapy, and social work.

Different types of stroke units are available: the acute stroke unit, the combined acute and rehabilitation stroke unit, the rehabilitation stroke unit and the mobile stroke team, established for hospitals where stroke units are not available. In combined stroke units and in rehab-type stroke units, patients are treated for longer periods, sometimes for the whole hospitalization phase after stroke. It is this type of stroke units for which efficacy has been proven in randomized trials and in meta-analyses.

Main indications for admission to an acute stroke unit are

- acute stroke which was symptomatic less than 24 hours
- instable or progressive neurologic deficit (all stroke patients)
- need for specific therapy (see above)
- need for early rehabilitation

### *Recommendations*

- Stroke patients should be treated on stroke units (LoE I)
- Stroke units should provide co-ordinated multidisciplinary care provided by medical, nursing and therapy staff who specialise in stroke care (LoE I)

## **Treatment of Acute Complications**

### **a) Ischaemic Oedema and Elevated Intracranial Pressure**

Focal brain oedema occurs during the first 24-48 hours after ischaemic infarcts. In younger patients or in patients with large MCA infarcts, oedema may lead to elevated intracranial pressure (ICP) with risk of herniation, secondary damage of central nervous tissue and impairment of vital functions.

#### **Medical Therapy**

Basic management includes head positioning at an elevation of up to 30°, avoidance of noxious stimuli, pain relief, appropriate oxygenation, normalizing body temperature.

If ICP monitoring is available, cerebral perfusion pressure should be kept >70 mmHg.

Although strong evidence is lacking, osmotherapy with 10% glycerol usually given intravenously (4 x 250ml over 30-60 minutes) or intravenous mannitol, (25-50g every 3-6 h) is the first medical treatment.

Hypertonic saline solutions given intravenously (5 x 100 ml Saline 3%), are probably similarly effective.

Short-acting barbiturates such as thiopental given as a bolus (250-500 mg) can quickly and significantly reduce ICP, but the effect may be exploited only to treat acute crisis.

Corticosteroids are not useful for brain oedema treatment after stroke.

#### **Hypothermia**

Effective lowering of ICP and protective effects by mild hypothermic treatment (33-35°C); should exclusively be used in centers with special expertise and neurocritical care facilities

#### **Surgery**

In prospective case series, surgical, decompressive therapy in hemispheric space-occupying infarction lowered mortality significantly without increasing the rate of severely disabled survivors. Early decompressive surgery within the first 24 h after stroke onset can reduce mortality even more markedly.

Ventriculo-stomy to reveal hydrocephalus and decompressive surgery is considered the treatment of choice for a space-occupying cerebellar infarction, although the scientific basis for this is not more solid than for hemispheric infarction. Like in supratentorial infarction, the operation should be performed before signs of herniation are present.

#### **Recommendations**

- Osmotherapy is recommended for patients whose condition is deteriorating secondary to increased intracranial pressure, including those with herniation syndromes (LoE IV)

- Ventriculo-stomy or surgical decompression and evacuation of large cerebellar infarctions that compress the brain stem is justified (LoE III)
- Surgical decompression and evacuation of a large hemispheric infarction can be a life-saving measure and survivors may have a residual neurological deficit that allows an independent life (LoE III)

### **b) Aspiration and Pneumonia**

Bacterial pneumonia is one of the most important complications in stroke patients, the majority being caused by aspiration

### **c) Urinary Tract Infection**

Urinary retention is frequent in the early phase after stroke and will require insertion of a urine catheter or supra-pubic catheter. Otherwise, the majority of hospital-acquired urinary tract infections are associated with the use of indwelling catheters.

### **d) Pulmonary Embolism and DVT**

The incidence of symptomatic PE and deep vein thrombosis is now <5% presumably reflecting modern clinical practice and admission to a stroke unit. The risk of deep venous thrombosis and pulmonary embolism can be reduced by early hydration, and early mobilisation.

### **e) Decubital Ulcer**

Frequent turning of immobilised patients is useful for prevention of decubital ulcers.

### **f) Seizures**

In the early phase of stroke, partial or secondary generalized epileptic seizures may occur.

#### *Recommendations*

- Low dose subcutaneous heparin or low molecular weight heparins should only be considered for patients at high risk of DVT or PE (LoE II)
- The incidence of venous thromboembolism may be reduced through early re-hydration and mobilisation, and graded compression stockings (LoE IV)
- Infections after stroke should be treated with appropriate antibiotics.
- Aspiration pneumonia may not be prevented by naso-gastric feeding (LoE IV)
- Early mobilisation is helpful to prevent numerous complications after stroke including aspiration pneumonia, deep venous thrombosis and decubital ulcers (LoE IV)
- Administration of anti-convulsants to prevent recurrent seizures is strongly recommended (LoE III)
- Prophylactic administration of anticonvulsants to patients with recent stroke who have not had seizures is not recommended (LoE IV)

## Early Rehabilitation

Rehabilitation should be started as soon as possible, since rehabilitation can reduce the number of patients who are left dependent after stroke. The intensity of the actual program depends on the status of the patient and the degree of disability. If active rehabilitation is not possible (e.g. impaired consciousness), passive rehabilitation has to be performed in order to minimize the risk of contractions, joint pain, bedsores, and pneumonia.

### *Recommendations*

- Every patient should have access to evaluation for rehabilitation
- Rehabilitation should be initiated early after stroke (LoE I). Disabled patients should have access to structured care including institutional care
- Rehabilitation should be provided by a multidisciplinary team in a stroke unit (LoE I)
- Intensity and duration of rehabilitation should be optimal for each patient; new methods of rehabilitation should be used (e.g. repetitive training and forced use), ideally supplementary to established methods (LoE II)
- Patients with chronic symptomatic stroke should be supported in their social environment. This includes access to a family physician, evaluation of out-patient rehabilitation services, secondary prevention and support in psycho-social functioning (LoE II)

## V Primary Prevention

### Life Style and Risk Factor Modification

Primary prevention is aimed at reducing the risk of stroke in asymptomatic people. Several conditions and lifestyle factors have been identified, whose modification is known to reduce the risk of stroke:

#### Arterial Hypertension

Hypertension is the most prevalent and modifiable risk factor for stroke, and its treatment reduces the risk of stroke.

#### Diabetes Mellitus

Diabetes is recognized as an independent risk factor for ischaemic stroke. Although strict control of glucose levels in diabetes mellitus has not been proven to be associated with a decreased risk of stroke, it should be encouraged because of benefits in terms of other diabetic complications.

#### Hyperlipidaemia

The relationship of total serum cholesterol levels to coronary heart disease is well established but less clear concerning ischaemic stroke.

#### Cigarette Smoking

Cigarette smoking is an independent risk factor for stroke (up to 6-fold). Persons who stop smoking reduce their risk of stroke by about 50%.

## **Alcohol Consumption**

Moderate consumption (e.g. two glasses of wine per day) is associated with decreased risk of stroke, while heavy consumption increases the risk of ischaemic and haemorrhagic stroke.

## **Physical Activity**

Regular and vigorous physical activity seems to be inversely related with the risk of stroke. This may be mediated through beneficial effects on body weight, blood pressure, serum cholesterol, and glucose tolerance.

## **Diet**

A low salt, low saturated fat, high fruit and vegetable diet rich in fibre is recommended (LoE II). Subjects with an elevated body mass index should take a weight reducing diet (LoE II).

## **Hormone Replacement**

Hormone replacement therapy (oestrogen / progestogen) should not be used for primary prevention of stroke (LoE I).

## **Recommendations**

- Blood pressure measurement is an essential component of regular health care visits. Blood pressure should be lowered to normal levels (<140/<90 mm Hg, or <135/80 mm Hg in diabetics) by means of lifestyle modification. Most hypertensive patients will also need pharmacological treatment to achieve normal blood pressure (LoE I)
- Although strict control of glucose levels in diabetes mellitus has not been proven to be associated with a decreased risk of stroke, it should be encouraged because of benefits in terms of other diabetic complications (LoE III)
- Cholesterol-lowering therapy (simvastatin) is recommended for high-risk patients (LoE I)
- Cigarette smoking should be discouraged (LoE II)
- Heavy use of alcohol should be discouraged, light or moderate alcohol consumption may be protective against stroke (LoE I)
- Regular physical activity is recommended (LoE II)

## **Antithrombotic Drugs and Anticoagulation**

### **ASA**

In asymptomatic patients, there is no scientific evidence for prescribing aspirin to reduce risk of stroke. However, the risk of myocardial infarction is reduced (LoE I). Asymptomatic patients with greater than 50% ICA stenosis should receive aspirin in order to reduce the risk of MI (LoE IV).

Other antiplatelet drugs are not recommended for primary stroke prevention (LoE IV).

### **Anticoagulation**

Asymptomatic patients with atrial fibrillation (AF), especially those with high risk due to concomitant heart disorders such as heart failure and valvular disorders, should receive antithrombotic primary prevention according to following *recommendations*:

- Long-term oral anticoagulation therapy (target INR 2.5; range 2.0-3.0) should be considered for all AF patients at high risk of embolism: age >75 years, or age >60 years plus risk factors such as high blood pressure, left ventricular dysfunction, diabetes mellitus (LoE I)
- Long-term aspirin (325 mg per day) or warfarin are recommended for patients with non-valvular AF at moderate risk for embolism: age 60-75 years without additional risk factors (LoE I)
- Warfarin is recommended for AF patients aged 60-75 with diabetes or coronary heart disease (LoE I) Although not yet established by randomised studies, in patients over 75 years, warfarin may be used with a lower INR (target INR of 2.0; range 1.6-2.5) to decrease the risk of haemorrhage (LoE III) Patients with AF unable to receive oral anticoagulants should be offered aspirin (LoE I)
- Long-term aspirin (325 mg per day) or no therapy are recommended for patients with nonvalvular AF at low risk for embolism: age < 60 years without additional risk factors (LoE I)

- Patients with AF who have prosthetic heart valves should receive long-term anticoagulation with a target INR based on the prosthesis type, but not less than INR 2-3 (LoE II)

### **Surgery and Endovascular Treatment for Asymptomatic Carotid Stenosis**

The results of trials assessing carotid endarterectomy (CEA) in asymptomatic patients are still a matter of controversy so that this therapy is not generally recommended for those patients. Only patients with a carotid stenosis greater than 60%, low surgical risk (< 3%), and with a life expectancy of at least five years are likely to benefit from surgery. A subgroup analysis of Asymptomatic Carotid Atherosclerosis Study (ACAS) indicates that women have significantly lower benefit from surgery than men.

#### *Recommendations*

- Carotid surgery may be indicated for some asymptomatic patients with a 60-99% stenosis of the ICA. The CEA-related risk for stroke or death must be less than 3%, and patients with a life expectancy of at least 5 years (or under the age of 80) may benefit from surgery (LoE II).
- Carotid angioplasty, with or without stenting, is not routinely recommended for patients with asymptomatic carotid stenosis. It may be considered in the context of randomised clinical trials.

## VI Secondary Prevention

### Risk Factor Modification

#### Antihypertensive Treatment

After stroke or TIA, blood pressure should be lowered, irrespective of its level, with a diuretic and/or an ACE inhibitor, subject to toleration of the treatment (LoE I). The effectiveness of other classes of BP lowering drugs has not yet been established by controlled trials

#### Cholesterol Lowering Therapy

Patients with a history of ischaemic stroke or TIA should be considered for statin (simvastatin) therapy (LoE I).

#### Smoking

All smokers should stop smoking, especially the patients who had stroke (LoE IV).

#### Hormone Replacement Therapy (HRT)

There is no indication to use HRT for secondary stroke prevention in postmenopausal women (LoE II).

### Antithrombotic Drugs and Anticoagulation

Antithrombotics as well as anticoagulants have been proven to reduce effectively the risk of recurrent ischaemic stroke. According to the studies received to date, following **recommendations** can be made:

### Antithrombotic Drugs

- Appropriate antiplatelet therapy should be given to prevent stroke recurrence and further vascular events (LoE I). There are three treatment options, that may all be considered as first choice depending on patient characteristics
- Aspirin (50 to 325 mg) should be given to reduce stroke recurrence (LoE I)
- Where available, the combination of Aspirin (50mg) and long release Dipyridamole (200mg twice daily) can be given as first choice to reduce the risk of stroke recurrence (LoE I)
- Clopidogrel is slightly more effective than ASA in the prevention of further vascular events (LoE I). It may also be prescribed as first choice or when Aspirin and Dipyridamole are not tolerated (LoE IV), and in high risk patients (LoE III).
- Patients with TIA or ischaemic stroke and unstable angina or non Q wave myocardial infarction should be treated with a combination of clopidogrel 75mg and ASA 75mg (LoE III)
- Patients starting treatment with thieno-pyridine derivatives should receive clopidogrel instead of ticlopidine because it has fewer side-effects (LoE III)
- In patients who cannot be treated by aspirin or thienopyridine derivatives, long release dipyridamole alone (200mg twice daily) may be used as an alternative (LoE II)

## Anticoagulation

- Oral anticoagulation (INR 2.0-3.0) is indicated after ischaemic stroke associated with atrial fibrillation (LoE I). Oral anticoagulation is not advisable in patients with comorbid conditions such as falls, epilepsy, severe dementia, or gastro-intestinal bleedings
- Patients with prosthetic heart valves should receive long-term anticoagulation therapy with a target INR between 2.5 and 3.5 or higher (LoE II)
- Patients with proven cardio-embolic stroke should be anticoagulated, if the risk of recurrence is high, with a target INR between 2.0 and 3.0 (LoE III)
- Anticoagulation should not be used after non-cardio-embolic ischaemic stroke, except in some specific situations, such as aortic atheromas, fusiform aneurysms of the basilar artery or cervical artery dissection (LoE IV)

## Surgery and Endovascular Treatment

Carotid endarterectomy (CEA) in symptomatic patients may be performed according to the following **recommendations** (valid only for centers with a perioperative complication rate of less than 6%):

- Conventional angiography, or one or ideally more of the following investigations - ultrasonography, magnetic resonance angiography (MRA), or CT angiography - may be used to identify and quantify carotid artery stenosis.

- CEA is indicated for patients with stenosis of 70-99% without a severe neurological deficit with recent (<180 days) ischaemic events. This is valid only for centres with a perioperative complication rate (all strokes and death) of less than 6% (LoE I).
  - CEA may be indicated for certain patients with stenosis of 50-69% without a severe neurological deficit. This is valid only for centres with a perioperative complication rate (all strokes and death) of less than 6%. The subgroup of patients most likely to benefit from surgery is males with recent hemispheric symptoms (LoE III)
  - CEA is not recommended for patients with a stenosis less than 50% (LoE I)
  - CEA should not be performed in centres not exhibiting low complication rates similar to those seen in NASCET or ECST (LoE I)
  - Patients should remain on antithrombotic therapy before, during and after surgery (LoE II)
  - Patients should be followed-up by the referring physician as well as the surgeon (LoE IV)
- Carotid stenting has not been proven to be equivalent or even superior to CEA, neither for symptomatic nor for asymptomatic patients.

### *Recommendations*

- Carotid PTA may be performed for patients with contraindications to CEA or with stenosis at surgically inaccessible sites (LoE IV)
- Carotid PTA and stenting may be indicated for patients with re-stenosis after initial CEA or stenosis following radiation (LoE IV).

- Patients should receive a combination of clopidogrel and aspirin immediately before, during and at least 1 month after stenting (LoE IV)



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