European Stroke Initiative
Recommendations for Stroke Management

European Stroke Initiative

For the European Stroke Initiative Executive Committee:
Werner Hacke, Heidelberg Germany
Markku Kaste, Helsinki Finland, Tom Skyhøj Olsen, Copenhagen Denmark,
Jean-Marc Orgogozo Bordeaux France, Julien Bogousslavsky Lausanne
Switzerland

Organisation of Stroke Care: Education, Referral, Emergency
services and Stroke Units

Acute stroke is one of the leading factors of morbidity and mortality world-wide. After
cardiovascular disease and cancer, stroke is the third most common cause of death
in industrialised countries.

In Europe, the crude death rate ranges from 63.5/100,000 (males, Switzerland 1992)
to 273.4/100,000 (females, Russia 1991). In addition, stroke is the most important
cause of morbidity and long term disability in Europe imposing an enormous
economic burden. In the UK, stroke accounts for nearly 5% of National Health
Service expenditure and 6% in Finland (Fogelholm et al 2001) (Isard & Forbes
1992). In 1990 the average cost of hospital treatment for a stroke survivor was GBP
7,500 in the UK (Forbes 1993), but in many European countries it is much higher.
The average direct cost from first stroke to death has been estimated as USD
79,000 in Sweden (Asplund et al 1993). Moreover, treatment for stroke is far from
satisfactory. Over the past decades, acute stroke has increasingly been recognised
as a medical emergency. Acute, postacute, and rehabilitation care of stroke patients
in specialised wards as well as revascularising therapies have been proven to be
effective in acute ischaemic stroke.

There have been several publications of guidelines or consensus papers over the
past years (Brainin, European Federation of Neurological Societies Task Force 1997;
Aboderin et al 1996; Adams et al 1994; European Ad Hoc Consensus Group 1996;
Biller et al 1998; Einhäupl et al 1999; Feinberg et al 1994; Gorelick et al 1999; Report
on Pan European Consensus Meeting on Stroke Management 1997; WHO Task
Force on Stroke and other Cerebrovascular Disorders 1989). This new
recommendation is proposed by the European Stroke Initiative (EUSI), the common
body of three major European neurological or stroke-related societies, the European
Neurological Society (ENS), the European Federation of Neurological Society
(EFNS) and the European Stroke Council (ESC), which also represents the
European Stroke Conference. In the EUSI recommendation, the authors provide
both, an overview of established or widely used therapeutic strategies as well as an evaluation of involving, but not yet proven strategies. Table 1 summarises the definitions for levels of evidence and classes of recommendations used in this article.

Education

**Stroke as an emergency**

Successful stroke care begins with recognising stroke as a medical emergency like acute myocardial infarction (MI) or severe pulmonary embolism. There is widespread consensus among stroke physicians, that the best way to provide early stroke care is to call the emergency medical system (EMS) immediately and to get transported to an institution, where stroke care can be provided on an adequate level. Unfortunately, EMS organisation varies from country to country and sometimes within countries. A uniform calling system, comparable to the US 911-system, and a improved training for dispatchers is most desirable.

Despite the high mortality and morbidity of stroke, many patients and relatives do not recognise the symptoms of stroke or realise that seeking treatment is urgent. Various factors are responsible for delay in patient referral to hospital including a poor awareness of stroke by the victim or family, reluctance to seek emergency medical help, incorrect diagnosis by the paramedical service and rating stroke as a non-emergency by medical personnel and the family physician. These facts emphasise the need for an ongoing education program. Primary contact with general practitioners may cause delays and prevent early institution of adequate therapy (Kothari et al 1997). Teaching the public about symptoms and signs of stroke is one of the highest priorities of public medical education.

Professional groups who must be motivated in stroke care include neurologists, internists, geriatricians, family doctors and emergency medicine physicians, other specialists, nurses, general practitioners and EMS personnel. The medical personnel should be trained in recognising the acute presentations of ischemic stroke and should be able to cope with the early complications after stroke. Emergency medical personnel should be trained to conduct a focussed neurological examination that includes level of consciousness, presence of focal weakness, presence of seizure activity and the presence of aphasia or other cognitive disturbances. It is particularly important that these groups learn that they are important and competent partners in providing acute stroke care.
Referral

Stroke patients should be referred to specialised centers (Stroke Unit Trialists Collaboration 1997) such as stroke units. Minimum requirements of such centers include 24-hour availability of CT scanning and neurologists or other stroke physicians, presence of specialised staff and adherence to treatment and management guidelines. Stroke centres and stroke units are no stand-alone solutions. They can only work optimally, if a well-established referral and rehabilitation network is available. This also includes co-operation with primary care physicians in primary and secondary prevention.

For optimal acute stroke care, it is essential that all stroke patients are immediately referred to the hospital best equipped to provide the most appropriate acute stroke. This may not necessarily be the nearest hospital. While all stroke patients seem to benefit from stroke unit treatment (Langhorne and Dennis 1993), certain subgroups of patients may especially benefit from intensive care unit treatment (European Ad Hoc Consensus Group 1997). Triage may be necessary and is recommended by the Stroke Council of the AHA, the American College of Physicians, and the European Ad Hoc Consensus Group.

Stroke Units

Stroke care should take place in a stroke unit. A meta-analysis by the Stroke Unit Trialist’s collaboration (Langhorne and Dennis 1993) showed a 18% reduction in mortality, a 29% reduction in death or dependence and a 25% reduction in death or need of institutional care when treated in a stroke unit in comparison to a general medical ward (level I). In a large randomized Norwegian trial of patients treated in the acute and subacute state (Rønnig and Guldvog 1998) mortality was reduced by 46% compared to general ward treatment.

A stroke unit is a hospital unit or part of a hospital unit that exclusively or nearly exclusively takes care of stroke patients. The well trained staff and the multidisciplinary approach to treatment and care characterise the stroke unit. The core disciplines of such a multidisciplinary team are: medical treatment, nursing, physiotherapy, occupational therapy, speech and language therapy and social work. The optimal size of a stroke unit in terms of beds is not known. Stroke units with as little as six beds have shown effective.

Results from the Stroke Unit Trialists Collaboration (1997) indicate that all types of patients with stroke benefit from treatment and rehabilitation in stroke units: males and females, young and elderly stroke patients and patients with mild, moderate and severe strokes.

Stroke units are available in several categories: (1) The acute stroke unit admitting patients acutely and continuing treatment several days but usually less than 1 week.
(2) The combined acute and rehabilitation stroke unit admitting patients acutely and continuing treatment and rehabilitation for several weeks or months if necessary. (3) The rehabilitation stroke unit admitting patients after a delay of 1 or 2 weeks and continuing treatment and rehabilitation for several weeks or months if necessary. (4) A mobile stroke team is a mobile team offering stroke care and treatment to stroke patients at a variety of wards. Such teams are usually established in hospitals where stroke units are not available. Of these only the combined acute and rehabilitation stroke unit and the rehabilitation stroke unit have proven effectiveness in terms of reduced mortality and handicap (Indredavik et al. 1997; and Dennis 1993).

Recommendations
1. Stroke patients should be treated in specialised stroke units (Level I).
2. Stroke needs to be considered as the medical emergency that requires public education, a referral and treatment network, and fast management.
3. In case stroke happens, the EMS should be called immediately. Patients should be transported by the EMS as fast as possible to qualified centres.

Management in the Emergency Room
Acute management of acute stroke requires parallel processes at different levels of patient management. For example, acute assessment of neurological and vital functions parallels treatment of acutely life-threatening conditions. Time is critical since the therapeutic window in a given patient may be quite narrow. The acute stroke patient, even the one with milder symptoms, must be considered as an urgently ill medical patient (Hacke et al. 1995; Brott et al. 1994; Brott and Reed 1989; Adams et al. 1994). Early assessment of stroke subtypes based on the physical and neurological evaluation, as well as skilled use and interpretation of diagnostic tests is essential (Saito et al. 1987). Factors delaying early intervention within the hospital include (1) admission policies that require placement of patients on general medical wards, (2) lack of access to early brain imaging facilities, (3). The rating of stroke as non-urgent by hospital staff, (4) lack of treatment facilities for stroke and (5) unavailability of a neurologist or another physician with special expertise in stroke in the emergency room.

Written protocols for the management of stroke patients are a prerequisite for standardised patient care. The thresholds for intervention in physiological parameters, e.g. blood glucose levels, oxygenation, or blood pressure (BP), should be set on an individual patient basis.

The initial examination includes observation of breathing function, assessment of BP and heart rate, and determination of arterial O₂ saturation using infrared pulse
oxymetry, if available. Simultaneously, blood samples for clinical chemistry, coagulation, and haematology studies are drawn, and a venous line is inserted. After the emergency assessment, which in part will be done by emergency nurses or other emergency room personnel, the neurologist should perform a targeted neurological examination.

Emergency diagnostic tests
Diagnostic tests are needed to differentiate between the different types of acute stroke, e.g. ischaemic, brain haemorrhage or subarachnoid haemorrhage (SAH), to rule out other brain diseases, to get an impression about the underlying cause of brain ischaemia, to provide a basis for physiological monitoring of the stroke patient and to identify concurrent diseases or complications associated with stroke that may influence prognosis.

Cranial Computerized Tomography (CT)
CT reliably distinguishes between haemorrhagic and ischaemic stroke. CT sings of early ischaemia can be detected as early as 2 hours after stroke onset (von Kummer et al 1997), but they may also develop later. Very extensive early infarct signs in the first hours after stroke indicate a very serious ischaemia with a higher risk of secondary haemorrhage or of large oedema formation. Brain haemorrhages are identified almost immediately, but they may grow in the first hours and, therefore, a second CT scan may become necessary. In addition, CT may detect subarachnoid blood in the majority of cases with SAH. While CT usually detects large infratentorial haemorrhages or cerebellar infarcts, smaller infarcts in the brainstem may be missed. CT also helps to identify other neurological disease that may be confused with stroke.

Magnetic Resonance Imaging (MRI)
MRI is more sensitive, also it has not yet reached the level of a standard procedure in most centers. Modern MRI techniques such as magnetic resonance angiography, diffusion MRI and perfusion MRI require major resources that are currently not available in a majority of centres.

Other Emergency Tests
An electrocardiogram should be performed in all stroke patients because of the high incidence of heart involvement in stroke patients. Stroke and acute MI may occur together. Hemispheric stroke may cause arrhythmias, subendocardial infarction and heart failure. Frequently, arrhythmias are the cause of embolic stroke.
Ultrasound studies are frequently performed in stroke centres throughout Europe. They include not only cw-Doppler or duplex sonography of the extra-cranial cervical arteries, but also trans-cranial Doppler. They are used to identify vessel occlusion, state of collaterals, or recanalisation. Other ultrasound studies include trans-thoracal and trans-oesophageal echocardiography to screen for cardiogenic emboli, but these studies are usually not performed in the emergency unit. However, it seems to be useful to have these studies available in the first 24 h after stroke onset.

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

Recommendations
1. A cranial CT is the most important diagnostic tool in patients with suspected stroke.
2. Early evaluation of physiological parameters, blood chemistry and haematology, and cardiac function is recommended in the management of acute stroke patients; this also includes ECG, pulsoximetry and chest x-ray.
3. Ultrasound of the extra- and intra-cranial vessels, modern MR techniques, cardiac ultrasound and special haematological and serological studies for rare causes of stroke should be performed early after stroke, but should not delay general or specific treatment.

Acute Stroke Management
There are three mainstays in the treatment of acute stroke. The first one is the treatment of general physiological conditions that need to become optimised in the setting of an acute stroke. This is usually referred to as "general therapy". The second is the specific therapy that directed against aspects of stroke pathogenesis, either recanalisation of a vessel occlusion or prevention of several mechanisms of neuronal injury that happen after brain ischaemia (neuroprotection). The third main part of stroke treatment is the treatment of complications which may either be neurological (such as secondary haemorrhage, space-occupying oedema or seizures) or medical (such as infections, decubital ulcers, deep venous thrombosis DVT or pulmonary embolism).
General stroke treatment

Monitoring of Vital Neurological and Functions on the Stroke Unit or in a Normal Ward

In all stroke patients neurological status and vital functions (BP, pulse rate, oxygenation, and temperature) should continuously or discontinuously monitored. The neurological status is best monitored using validated neurological scales, such as NIH Stroke Scale, the Scandinavian Stroke Scale, the Glasgow Coma Scale and others. In selected cases with pre-existing cardiac disease, history of arrhythmias and unstable BP by ECG-monitoring is desirable. The electrodes for cardiac monitoring can also be used for respiratory monitoring. The respiratory status is checked clinically if there is no continuous monitoring. Blood pressure monitoring can be performed discontinuously using repetitive automatic inflatable sphygmonometer or with a mobile 24-hour blood pressure monitoring device. Most of the times, conventional BP monitoring is adequate. Pulse oxymetry is frequently used for continuous monitoring on stroke units. It provides relevant information on the patient’s respiratory status. A central venous catheter and occasionally central venous pressure monitoring is needed in severe stroke patients treated in specialised wards. Via a central venous catheter, indirect information on intra-vascular volume, cardiac function, and compliance within the venous system can be achieved.

In most stroke patients, the acute neurological symptoms are prominent, but treatment and prognosis are co-determined by underlying and associated systemic diseases that are almost always present. The term "general treatment" means to provide an optimum physiological basis upon which specific therapeutic treatment strategies follow. There is consensus that the management of general medical problems is the basis for stroke treatment (WHO Tasks Force 1989; Brott and Reed 1989; Adams et al 1994; Hacke et al 1995; European Ad Hoc Consensus Group 1996). General management of stroke patients comprises respiratory and cardiac care, fluid and metabolic management, BP control, and perhaps treatment of elevated intra-cranial pressure. In addition, treatment of seizures and prophylactic measures concerning DVT, pulmonary embolism, aspiration pneumonia, other infections, and decubital ulcer are part of the general treatment of the patients. Most authors agree that adequate treatment and preservation of vital functions constitute the basis of all therapeutic measures in acute stroke not only on stroke units, but also in normal wards. On the other hand, one has to keep in mind that even the proposed management of hypertension or hyperglycaemia in stroke has never been tested prospectively.
**Pulmonary Function and Airway Protection**

Like in the emergency room, adequate blood oxygenation with normal respiratory function is required for stroke management, although there is no convincing prospective clinical evidence that oxygen supply at low flow rates is useful in human brain infarction. Adequate oxygenation may be important for the preservation of metabolic turnover in the marginal zone of the insult, the so-called penumbra. The oxygenation of the blood is improved by the administration of 2-4 liters $O_2$/min via a nasal tube.

A threatened airway may be found in patients with brainstem infarction in patients with reduced level of consciousness, brain haemorrhage or in patients with seizure activity following hemispheric stroke. Overt pulmonary dysfunction is occasionally present in the form of slightly exacerbated chronic obstructive airway disease. Ventilation may be particularly compromised during sleep.

In the event of a pathological respiratory pattern, most likely found in patients with extensive vertebrobasilar and hemispheric infarction or with large intracranial haemorrhages, and in the unconscious patient at high risk for aspiration pneumonia, early endotracheal intubation is recommended. Of course, before intubation is performed, the general prognosis, co-existing life-threatening medical conditions and the presumed will of the patient and his family have to be taken into account. On the other hand, prognosis of stroke patients undergoing intubation is not as bad as assumed with a 1-year survival rate of almost one third of the patients (Grotta et al 1995; Steiner et al 1997).

**Cardiac Care**

Cardiac arrhythmias secondary to stroke are not unusual. Significant alterations in the ST segments and the T-waves on the ECG may appear in the acute phase mimicking myocardial ischemia because of subendocardal infarction (Norris 1983). Cardiac enzymes may be elevated after stroke (Kaste et al 1978). Every stroke patient should have an initial ECG. However, not all cardiac phenomena after cerebral ischaemia should be regarded as secondary. There is a coincidence of MI, sometimes not particularly clinically impressive, with cerebral ischaemia (Furlan 1987).

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 $H_2O$, and its monitoring, although not frequently used on a normal ward, will give early warning of a volume deficiency or volume overload, which both have negative effects on cerebral perfusion. The intravascular volume must be kept stable. Among the inotropic agents, dobutamine has the advantage of increasing cardiac output without substantially affecting either heart
rate or BP. Dopamine may be particularly useful in patients with hypotension or renal insufficiency. Increases in cardiac output may increase cerebral perfusion in areas, which have lost their autoregulative capacity after acute ischaemia. Restoration of normal cardiac rhythm using drugs, cardioversion, or pacemaker care should be performed in cooperation with internists or cardiologists.

**BP Management**

BP monitoring and treatment is a critical issue. Many patients with acute infarcts have elevated BP. Furthermore, cerebral blood flow autoregulation may be defective in an area of evolving infarction so that flow in the critical penumbra zone is passively dependent on the mean arterial pressure. Drops in BP must be avoided if an adequate cerebral perfusion pressure is to be maintained. A target systolic BP of 180 mm Hg and diastolic BP of 100-105 mm Hg is recommended in patients with prior hypertension. In other cases, mild hypertension is desirable (160-180/90-100 mm Hg). Obviously, this does not apply to extremely high BP levels. Systolic values over 220 mm Hg or diastolic values over 120 mm Hg (in some centres, especially in North America, thresholds of 240 (systolic) and 130 (diastolic) are accepted) constitute an indication for early drug treatment, but even here the reduction in BP should not be too drastic. Table 2 gives an overview of frequently used anti-hypertensive drugs after stroke.

There are only few other indications for immediate anti-hypertensive therapy in the first hour after symptom onset. Treatment may be appropriate in the setting of acute myocardial ischemia (although extreme lowering of BP is negative for MI-patients, too), cardiac insufficiency, acute renal failure, or acute hypertensive encephalopathy. In case the CT scan has shown a non-ischemic cause of stroke, such as SAH or intracerebral haemorrhage, antihypertensive treatment may also be started.

The effects of oral nifedipine, still frequently used in Europe, may be rapid and excessive. Its use is discouraged. Oral captopril, 6.25-12.5 mg, may be used instead. In North America and in some European countries intravenous labetalol (10 mg) is frequently recommended. Increasingly intravenous urapidil is used in this situation. Finally, sodium nitroprusside is sometimes recommended despite some major side-effects, such as reflex tachycardia and coronary artery ischaemia.

**Glucose Metabolism**

Many stroke patients are diabetics. Sometimes diabetes mellitus (DM) is discovered for the first time after an ischaemic infarct has developed. A pre-existing diabetic metabolic derangement may be dramatically worsened in the acute phase of stroke, and temporary insulin treatment may become necessary. High glucose levels are not advantageous in stroke (Pulsinelli et al 1983). A blood glucose of 10 mmol/l or higher
requires immediate insulin titration. Unless the blood glucose is known, no carbohydrate concentration should be given to a stroke patient. Hypoglycaemia can rarely mimic an acute ischaemic infarction. Hypoglycaemia should be directly antagonised by infusion of 10-20% glucose, preferably via a central venous line.

**Body Temperature**
Fever negatively influences neurological outcome after stroke (Castillo et al 1998; Reith et al 1996). Infection is a risk factor for stroke, and many patients develop in an infection after stroke (Grau et al 1995). Experimentally, fever increases infarct size. Although there are no controlled trials to support this, it seems to be sensible, to treat an elevated temperature in stroke patients. Antipyretics such as paracetamol and the early use of antibiotics in case of apparent bacterial infection are usually recommended. Although there are no prospective data, one may consider to treat fever as early as the temperature reaches 37.5°C.

**Fluid and Electrolyte Management**
Serious electrolyte abnormalities are rarely noted after ischaemic stroke. They frequently occur after massive intracerebral haemorrhage and SAH (Diringer et al 1988). Stroke patients should have a balanced fluid and electrolyte status to avoid plasma volume contraction, raised haematocrit, and impairment of rheologic properties of the blood. The electrolytes should be monitored daily and substituted accordingly. Uncontrolled volume replacement may lead to pulmonary oedema and cardiac failure and may increase cerebral oedema. An intravenous access is needed for initial fluid management and blood sampling. If larger volumes of fluids need to be replaced or solutions with high osmolality are used, placement of a central venous catheter is recommended.

**Recommendations**
1. Neurological status and vital functions should be monitored.
2. Glucose and body temperature should be monitored and corrected, if elevated (level III).
3. Monitoring and correction of electrolyte disturbances are advised.
4. Secure airways and supply oxygen to patients with severe acute stroke (level III).
5. Do not treat hypertension in patients with ischaemic stroke, if they do not have critically elevated BP levels (level III).
Specific Treatment

Thrombolytic Therapy

Thrombolytic therapy with recombinant tissue plasminogen activator (rtPA 0.9 mg/kg body weight given within 3 h after stroke onset to patients with acute ischaemic stroke) significantly improves outcome after stroke (National Institute of Neurological Disorders and Stroke, 1995). This treatment is not yet approved in Europe, except in Germany, in contrast to North America. There is evidence that thrombolysis may also work up to 6 h after stroke onset in carefully identified patients (Hacke et al 1998). In Europe, there is still some doubt about its risk-benefit ratio, which prevents some centres from actively promoting this treatment. Caution is advised before giving intravenous rtPA to persons with severe stroke (NIH Stroke Scale >22) and with extended early infarct signs (von Kummer et al 1997). In centres, where thrombolytic therapy is offered, it should only be given if the diagnosis is established by a physician who has expertise in the diagnosis of stroke, and a CT of the brain is assessed by physicians who have expertise in identifying major early infarct signs, which may represent a contra-indication against intravenous thrombolysis.

Because thrombolytic drugs carry the risk of major bleeding, the risks and potential benefits of rtPA should be discussed with the patient and family before treatment is initiated. Recognition of early infarct signs and strict adherence to exclusion criteria is essential.

Intravenous streptokinase has been shown to be associated with an unacceptable risk of haemorrhage and haemorrhage-associated death (Multicenter Acute Stroke Trial, Italy, MAST-I, 1996, Multicenter Acute Europe Stroke Trial, MAST-E, 1996) and is strongly discouraged.

Intra-arterial thrombolytic therapy of occlusions of the proximal part of the middle cerebral artery (MCA) using pro-urokinase has been shown to be significantly associated with a better outcome in a recently published randomised trial. This treatment requires super-selective angiography and is only available in selected centres (Furlan et al 1999). The treatment is safe and efficacious in a 6-hour time window.

Intra-arterial treatment of acute basilar occlusion with urokinase or rtPA is used in selected centres, but has not been subjected to a randomised trial (Hacke et al 1988; Brandt et al 1996).

Defibrinogenating enzymes

Ancrod, a defibrinogenating enzyme has been shown to improve outcome after acute ischaemic stroke, if given within three hours after stroke onset and over five days (Sherman 1999). However, a European trial testing ancrod treatment in a 6-hour time window was terminated prematurely.
Recommendations for centres offering thrombolysis

1. Intravenous rtPA (0.9 mg/kg; maximum of 90 mg), with 10% of the dose given as a bolus, followed by an infusion lasting 60 minutes, is recommended treatment within three hours of onset of ischaemic stroke (level I).

2. The benefit from the use of intravenous rtPA for acute ischaemic stroke >3 h after the onset of symptoms is smaller, but present in selected patients (level I).

3. Intravenous rtPA is not recommended when the time of onset of stroke cannot be ascertained reliably; this includes persons whose strokes are recognised upon awakening (level III).

4. Intravenous administration of streptokinase, outside the setting of a clinical investigation, is dangerous and not indicated for the management of persons with ischaemic stroke (level I).

5. Data on the efficacy or safety of any other intravenously administered thrombolytic drugs are not available to provide a recommendation.

6. Intra-arterial treatment of acute MI occlusion in a 6-hour time window using pro-urokinase results in a significantly improved outcome (level I).

7. Acute basilar occlusion may be treated with intraarterial therapy in selected centers (level IV).

8. Ancrod given in a 3-hour time window significantly improves outcome after acute ischaemic stroke (level I).

Platelet Inhibitors

The results of two very large randomised, not blinded intervention studies indicate that aspirin given within 48 h after stroke reduces mortality and the rate of stroke recurrence minimally, but statistically significantly (International Stroke Trial Collaborative Group 1997; Chinese Acute Stroke Trial, 1999). Whether the mild positive effect of early aspirin is due to an effect on the infarct itself or due to prevention of recurrent infarction is not yet clear.

Early Anticoagulation

Early anticoagulation has been frequently used in the treatment after acute ischaemic stroke. Unfortunately, none of the trials that has been performed in the past years have supported the idea that early heparin may influence outcome after ischaemic stroke or may at least reduce the number of recurrent strokes (Swanson 1999). While there was some kind of improvement in outcome or reduction in stroke recurrence rates, this was almost always counterbalanced by an increased number of haemorrhagic complications. In addition, most investigators nowadays agree that
heparin is not and never will be a standard therapy for all stroke subtypes, rather that high-risk patients (such as patients with stroke associated with atrial fibrillation (AF), for example), should be studied separately (Chamorro et al 1999). Table 3 gives some indications in which full dose intravenous heparin may currently be proposed. Contra-indications for the treatment with heparin include large ischaemic infarcts (e.g. more than 50% of MCA territory), uncontrollable arterial hypertension and advanced micro-vascular changes in the brain.

**Hemodilution**

The clinical benefit of haemodilution therapy has not been established, and the possibility of excess brain oedema has not been excluded (Strand et al 1992; Italian Acute Stroke Study Group 1988; Scandinavian Stroke Study Group 1987; Hemodilution in Stroke Study Group 1989).

**Neuroprotection**

Not a single neuroprotective agent has been shown to influence outcome after stroke. Currently, there is no recommendation to treat patients with neuroprotective drugs after ischaemic stroke.

**Recommendations**

1. There is no recommendation for general use of heparin, low-molecular-weight heparin or heparinoids after ischaemic stroke (level I).
2. Full-dose heparin may be used in selected indications such as AF, other cardiac sources with high risk of re-embolism, arterial dissection or high-grade arterial stenosis (level IV).
3. Aspirin 100-300 mg per day can be given after stroke to an unselected population, even without CT-scan (level I).
4. Haemodilution therapy is not presently recommended for the management of patients with acute ischaemic stroke (level I).
5. Currently, there is no recommendation to treat patients with neuroprotective drugs after ischaemic stroke (level I).

**Prevention and Treatment of Complications after Stroke**

**Aspiration and Pneumonia**

One of the most important risks in the early phase after stroke is aspiration pneumonia. Bacterial pneumonia accounts for 15-25% of stroke deaths. The majority of the pneumonias are caused by aspiration (Horner 1988). Aspiration is frequently found in patients with reduced consciousness, but also in patients with impaired gag
reflexes or with swallowing disturbances, which are not only found after brainstem stroke. A patients swallowing ability must be assessed before he/she is allowed to eat and drink. Nasogastric feeding may be helpful in the prevention of aspiration pneumonia although it does not completely reduce the risk. Once aspiration is seen, appropriate antibiotics should be considered. Other reasons of pneumonia include hypostatic pneumonia due to poor coughing and immobilisation. Frequent changes of the patient position in bed and pulmonary physical therapy may prevent this type of pneumonia.

**Urinary Tract Infection**

Urinary tract infection is the most common medical complication of acute cerebral infarction. Urinary retention is frequent in the early phase after stroke. The majority of hospital-acquired urinary tract infections are associated with the use of indwelling catheters. On the other hand, intermittent catheterization is not always feasible in the setting of severe stroke and may contribute to decubital ulcer. Suprapubic catheters are considered to carry lower risk of infection. Acidification may reduce the risk of infection, whereas intermittent catheterisation has not been shown to have a reduced risk. Once urinary infection is seen, appropriate antibiotics should be chosen. However, there is no need for prophylactic antibiotics.

**Pulmonary Embolism and DVT**

Pulmonary embolism maybe the cause of death in up to 5% of patients dying following ischaemic cerebral infarction, even in patients who otherwise would have had an excellent recovery from the stroke. The risk of DVT and pulmonary embolism can be reduced by early mobilisation and by the use of subcutaneous heparin or molecular-weight heparin. However, this effect seems to be counterbalanced by an increase of hemorrhagic complications (IST). Nevertheless, prophylaxis with subcutaneous low-dose heparin, 5,000-7,500 IU every 12 h or low molecular weight heparins has been recommended for bedridden stroke patients. Tachypnoea and pain are sensitive signs of pulmonary embolism (and of pneumonia). Examination of lower extremities should be performed daily to detect signs of DTV. Physical therapy and support stockings are suggested as an alternative.

**Decubital Ulcer**

Frequent turning of immobilised patients is useful for prevent decubitus. The skin of the incontinent patient must be kept dry. For patients at particularly high risk, an air- or fluid-filled mattress system should be used. If the decubitus does not respond to
conservative therapy, antibiotic therapy maybe justified for several days, preceding definitive surgical debridement.

**Seizures**
Partial (focal) or secondary generalized epileptic seizures may occur in the acute phase of ischaemic stroke. Clonazepam (2 mg i.v.) or diazepam 10-20 mg i.v.) followed by phenytoin or fos-phenytoin if i.v. phenytoin is not available either orally or i.v., or carbamazepin is the treatment of choice.

**Recommendations**
1. Administration of heparin or low-molecular-weight heparin in bedridden patients after stroke is recommended to reduce the number of DVT and pulmonary embolism; however, there is a risk of additional intracranial bleeding (level I).
2. Infections after stroke should be treated with appropriate antibiotics. Aspiration pneumonia may be prevented by testing patients swallowing ability naso-gastric feeding (level IV).
3. Early mobilisation is helpful to prevent numerous complications after stroke including aspiration pneumonia, DVT and decubital ulcers (level III).
4. Administration of anticonvulsants to prevent recurrent seizures is strongly recommended (level III).
5. Prophylactic administration of anticonvulsants to patients with recent stroke who have not had seizures is not recommended (level IV).

**Elevated Intracranial Pressure (ICP) and Brain Oedema**
Ischaemic brain oedema occurs during the first 24-48 h after ischaemic infarcts. In younger patients with complete MCA infarction, brain oedema and elevated ICP may become a major complication and may lead to herniation and death (Hacke et al 1996). These patients usually show a rapid decline in consciousness and develop signs of herniation 2-4 days after onset of symptoms. Outcome is fatal in the majority of these patients with a mortality of about 80% with standard treatment (Rieke et al 1995; Hacke et al 1996).

**Medical Therapy**
Basic management of elevated intra-cranial pressure following stroke includes head positioning at an elevation of less than 30°, avoidance of noxious stimuli, pain relief, appropriate oxygenation and normalising body temperature. Osmotherapy with 10% glycerol usually given intravenously (4 x 250 ml of 10% glycerol over 30-60 minutes)
or intravenous mannitol, 25-50 g every 3-6 h is the first medical treatment to be used if signs of space-occupying oedema occurs. Hypotonic and glucose-containing solutions should be avoided as replacement fluids. Dexamethasone and other corticosteroids are not useful for brain oedema treatment after stroke. Short-acting barbiturates such as thiopental given as a bolus can quickly and significantly reduce ICP. The effect is only short lived and allows the management of an acute crisis, e.g. prior to operation only. Barbiturate treatment requires ICP and EEG monitoring and careful monitoring of haemodynamic parameters, as a significant blood pressure drop may occur. Tris-(hydroxy-methyl-)aminomethane buffer solution or hypertonic NaCe-solution may be used as alternate treatment to glycerol or mannitol.

**Hypothermia**

Recently, Schwab et al (1998) showed that mild hypothermia with brain temperature between 33 and 35°C is safe and reduces the mortality rate in this group of patients. The number of patients is still too small to draw any decisive conclusions, however this method is feasible and will be tested prospectively in several institutional protocols.

**Decompressive Surgery**

**Malignant MCA Infarction**

The rationale of decompressive surgery is to allow expansion of the oedematous tissue to reduce ICP, to increase perfusion pressure, and to preserve cerebral blood flow by preventing further compression of the collateral vessels. In prospective case series, surgical, decompressive therapy in hemispheric space-occupying infarction lowers mortality from 80% down to 30% without increasing the rate of severely disabled survivors. Early decompressive surgery (e.g within the first 24 h after stroke onset) can reduce mortality even more pronounced (Riecke et al 1995; Schwab et al 1998). Prospective, multicenter study protocols have been recently developed and are underway.

**Cerebellar Infarction**

Ventriculostomy to reveal hydrocephalus and decompressive surgery is considered the treatment of choice of a space-occupying cerebellar infarction, although the scientific basis for this is not more solid than for hemispheric infarction. Comatose patients with space-occupying cerebellar infarctions have a mortality of about 80% if treated conservatively. This high mortality can be lowered down to less than 30% if decompressive surgery is performed (Heros 1992; Rieke et al 1993). Like in space-occupying supratentorial infarction, the operation should be performed before signs of herniation are present. The prognosis among survivors is very good, even if they
were comatose when the operation was performed. It should be noted, however, that these are the results of open, small or medium-sized case series, one of them being prospective (Rieke et al 1993), the remainder being mostly retrospective. Data from a controlled, randomised trial are lacking.

**Recommendations**

1. Osmotherapy is recommended for patients whose condition is deteriorating secondary to increased ICP, including those with herniation syndromes (level III).
2. Ventriculostomy or surgical decompression and evacuation of large cerebellar infarctions that compress the brain stem is justified (level III).
3. Surgical decompression and evacuation of a large hemispheric infarction can be a life-saving measure, survivors may have a residual neurological deficit that allows an independent life (level III).

**Rehabilitation after Stroke**

At least half of stroke patients have significant neurological impairments that limit independence and 20% of the patients are totally dependent. Rehabilitation can reduce the number of patients who are left dependent after stroke.

**Early Rehabilitation**

40% of stroke patients need active rehabilitation services. Rehabilitation of a stroke victim is started as soon as possible. This means that the patient should immediately be brought to a hospital with such facilities not only because of acute diagnosis and therapy but also because of early rehabilitation. The intensity of the rehabilitation program depends on the status of the patient and the degree of the disability. If the patient is unconscious the rehabilitation is passive to prevent contractions and joint pain, and to prevent distress for the patient when movement is restarted after immobilisation. With passive rehabilitation one can also minimise the risk of decubital ulcers and pneumonia. All joints on the paralysed side are moved through the full range of motion several times a day (3-4 times at least). Patients rarely need to be immobilised in bed for more than 1 or 2 days after the stroke unless they have a major decrease in the level of consciousness. Prolonged immobilisation and hemiplegia carries a risk of DVT and the complication of pulmonary embolism. After 2 or 3 days most patients who are alert can be moved out of bed with safety and placed in either a wheel chair or fixed chair for a good part of each day.
**Rehabilitation Programs**

Once the initial phase of stroke has passed, the patients should be carefully assessed for the degree of disability and a detailed rehabilitation program should be developed. The assessment of the patient’s situation includes evaluation of intellectual impairment including specific cognitive deficits such as aphasia, agnosia, apraxia, mood, motivation, the degree of motor weakness, sensory loss, and visual loss. Other problems that influence the patient’s ability to respond to rehabilitation include financial burden, chances of return to social activities and work, to live at home, sexual function, and the need of help.

Ideally, the multidisciplinary stroke team required to provide adequate rehabilitation for stroke victims includes (1) the stroke physician, (2) nurses experienced in stroke management, (3) a physiotherapist trained in stroke rehabilitation, (4) an occupational therapist skilled in stroke, (5) a speech therapist familiar with speech problems in stroke, (6) a neuropsychologist accustomed to stroke rehabilitation, and (7) a social worker familiar with the problems of stroke patients.

Of course most hospitals treating stroke patients do not have all these specially trained stroke experts. The core of the stroke team, physician, nurse and physiotherapist can be found in most hospitals and they can provide a decent rehabilitation program if they take it as a challenge.

The progress of the patient needs to be followed on a daily basis by the different members involved in his/her rehabilitation. The patients and the members of their family should be part of the stroke team. They should be taught the principles of stroke rehabilitation, and the members of the family also need to be taught when not to help the patient in order to optimise the progress of the rehabilitation plan. As soon as the patient's condition allows he/she should visit his/her home, to smooth the transit from hospital to home and increase the patient’s motivation to try his/her best in rehabilitation. If a patient needs a longer rehabilitation period they should be transferred to a special rehabilitation hospital if such a place is available. In this case, it is of utmost importance that all members of the stroke team transfer documentation of the patient's progress to the stroke team of the rehabilitation hospital. After institutional rehabilitation or if the patient does not need such care, the rehabilitation program can be taken over by the out-patient rehabilitation clinic if one exists locally.

The recovery of neurological deficit occurs fastest during the first 3 months after the onset of symptoms. This is also the optimal time for rehabilitation. Active rehabilitation, however, should be administered as long as objective improvement in the neurological dysfunction is observed.
After most of the improvement in neurological dysfunction has occurred and the active rehabilitation program has come to an end, the stroke patient needs a long-term rehabilitation program, which should include twice a year a series of 15-20 physiotherapy sessions. This is to guarantee that the functional status, which has been achieved during the acute rehabilitation program, is sustained. Should the functional outcome of a patient be in jeopardy, an active more comprehensive rehabilitation program is needed and sometimes it is reasonable to readmit the patient again for more intensive in-patient rehabilitation. Rehabilitation programs do not change the neurological deficit, but patients can become ambulatory and largely independent. Of more importance is the fact that majority of patients are able to be at home and do not require nursing-home care. A better outcome of stroke is of benefit in both human and economic terms. The Stroke Unit Trialists Collaboration and meta-analyses about stroke units have confirmed the value of systematic rehabilitation.

Recommendations
1. Rehabilitation should be initiated early after stroke (level I).
2. Every patient should have access to evaluation for rehabilitation (level III).
3. Rehabilitation services should be provided by a multidisciplinary team (level III).

Primary and Secondary Prevention
Primary prevention
Several conditions and life-style factors have been identified as risk factors for stroke. These include arterial hypertension, MI, AF, DM, elevated cholesterol levels, carotid artery disease, smoking, and alcohol use. Primary prevention is aimed at reducing the risk of stroke in asymptomatic people; recommendations concerning patients with transient ischaemic attacks and coronary heart disease (CHD) are considered here as secondary prevention. As mentioned above, modification of risk factors is known to decrease the incidence of stroke in asymptomatic people.

Hypertension
Hypertension is the most prevalent and modifiable risk factor for stroke, and its treatment substantially reduces the risk of stroke. A meta-analysis of 14 randomised trials showed a significant reduction of 42% in stroke in treated patients, with a decrease of only 5-6 mm Hg in the diastolic BP (Collins et al 1990). The Systolic Hypertension in the Elderly Program (SHEP) revealed that management of isolated systolic hypertension (> 160 mm Hg) in persons older than 60 years reduces the
total incidence of stroke by 36% (SHEP Cooperate Research Group 1991). The absolute benefit, estimated at 5 years, was 30 events per 1,000 participants. The optimal BP is not known, and there is some concern that a vigorous reduction in BP could be associated with increased cardiovascular morbidity - the J-curve concept. It should be mentioned that these results have been accomplished with anti-hypertensives such as diuretics and β-blockers and, most recently for ACE-inhibitors (HOPE trial 2000, PROGRESS Trial 2001). No prospective data exist for other classes of anti-hypertensives such as AT receptor blockers, clonidin or α-receptor blockers. It seems to be quite unlikely, that such effects would not be found with modern antihypertensive, too.

**Diabetes mellitus**
Although DM is recognized as an independent risk factor for ischaemic stroke, it is not established whether strict control of blood glucose prevents stroke. In fact, in patients with type 2 DM, intensive sulfonylurea and/or insulin therapy ameliorated microvascular systemic complications, but not macrovascular complications, such as stroke (UK Prospective Diabetes Study (UKPDS) Group 1998).

**Hypercholesterolemia**
Although the relationship of serum total cholesterol and CHD is well established, its relationship to stroke is not entirely clear. A recent meta-analysis did not find a strong association between serum cholesterol levels and stroke (Prospective Studies Collaboration 1995). Two large studies have demonstrated that they decrease the risk of stroke for patients with CHD (Sheperd et al 1995). The CARE study revealed a 32% reduction in the relative risk of stroke with pravastatin therapy and in the LIPID Study showed a 19% reduction (Plehn et al 1999; LIPID 1998). Moreover, a recent meta-analysis, including the data from the above trials, confirmed a 31% reduction in stroke, similar to the effects on CHD; however, there was no reduction in fatal stroke (Blaw et al 1997). In a meta-analysis of 16 trials, however, a 29% reduction of stroke and a 28% reduction in mortality was found in patients treated with statins.

**Cigarette Smoking**
Cohort studies have shown cigarette smoking to be an independent risk factor for ischemic stroke in both men (Abbott et al 1986) and women (Colditz et al 1988). The risks are depending on cigarette consumption and maybe as high as 6-fold compared with non-smokers. In both studies, subjects who stopped smoking considerably reduced their risk of stroke by about 50% (Colditz et al 1988).
**Alcohol Consumption**

The association between alcohol consumption and stroke is not linear. A recent case-control suggested that moderate consumption (up to 2 drinks of liquor, 2 cans of beer, or 2 glasses of wine per day (i.e. 20-30 g of ethyl alcohol) is associated with a decreased risk of ischemic stroke. Heavy alcohol consumption is associated with an increased risk of both ischaemic and haemorrhagic stroke (Hillman and Kaste 1978, 1982; Sacco et al 1999).

**Physical Inactivity**

Physical activity seems to be inversely related with the risk of stroke. A recent prospective cohort study of men participating in the Physician Health Study revealed that vigorous exercise was associated with a decreased risk of stroke (Lee et al 1999). The data suggested that this association was mediated through beneficial effects on body weight, BP, serum cholesterol, and glucose tolerance, and that, apart from these effects, physical activity had no influence on stroke incidence.

**Antithrombotic drugs**

Over the past decades, studies have shown that aspirin can definitely reduce the recurrence of cardiovascular events. Several large clinical trials have addressed the primary prevention of vascular events with aspirin. In the non-blinded British Male Doctor Study 5,139 physicians were randomly allocated to receive or not receive 500 mg of aspirin daily. There was no difference in the incidence of MI, but disabling strokes were more common among those allocated to aspirin (Peto et al 1988). Given the limited data on which of the strokes were thrombotic and which haemorrhagic, the higher incidence of strokes in the aspirin group is probably due to a higher incidence of haemorrhagic stroke.

The Physician’s Health Study was a randomized, double-blinded, placebo-controlled trial that analyzed data from 22,071 male physicians who received either 325 mg of aspirin or placebo every other day (Steering Committee of the Physicians’ Health Study Research Group 1989). The study demonstrated a 44% risk reduction of MI and a non-significant increased risk of stroke. In the subgroup with haemorrhagic strokes, aspirin was associated with an increased risk that was of borderline statistical significance.

In the Nurses’ Health Study cohort, in which the incidence of stroke in women taking aspirin was recorded, women taking aspirin had a smaller relative risk (0.68) of MI, but no alteration in the risk of stroke (Manson et al 1991).
Recommendations

1. BP measurement should be an essential component of regular health care visits. BP should be lowered to normal (135/85 mm Hg) values by means of life-style modifications and/or pharmacological treatment (level I).

2. Although the strict control of glucose levels in DM and of high cholesterol levels has not yet been proved to be associated with a decreased risk of stroke, it should be encouraged because of benefits in terms of other diseases (level III).

3. In coronary patients, treatment with simvastatin or pravastatin clearly reduces the risk of stroke (level II); statins should be prescribed in patients with CHD and high or moderate cholesterol levels. The benefits of statins probably extend to patients with stroke and high cholesterol levels.

4. Cigarette smoking should be discouraged (level II).

5. Heavy use of alcohol should be avoided, while moderate consumption may be permitted (level II).

6. Regular physical activity is recommended (level II).

7. There is no scientific support for prescribing aspirin to reduce the risk of stroke in asymptomatic patients (level I); however, aspirin may reduce the risk of MI in a asymptomatic population (level ).

Anticoagulation: AF

A recent review reported an average stroke rate of 5%/year among patients included in primary prevention trials, with a wide clinically important variation among subpopulations of AF patients (0.5-12%/year). Aggregate analysis of several trials shows that anticoagulation with the oral vitamin K antagonist, warfarin, reduces the rate of ischaemic stroke by 70% compared to that in untreated patients (AFASAK, SPAF, BAATAF, CAFA and SPINAF) (Laupacis et al 1998). Assessment of the optimal intensity of anticoagulation in the EAFT study showed that an anticoagulant therapy producing an international normalized ratio (INR) between 2.0 and 2.9 reduced the combined incidence rate for ischaemic and haemorrhagic events by 80% when compared to an INR below 2.0 (European Atrial Fibrillation Study Group 1995). When the INR was above 5.0, the risk of bleeding complications became unacceptable, whereas no significant reduction in thrombo-embolic events was seen at INR <2.0.

Aspirin was assessed in four randomized trials and yielded a pooled risk reduction of 21% compared to placebo (Hart et al 1998). In two of these trials, it was significantly less efficacious than warfarin.

Patients with AF and no other cardiovascular disease (“lone AF”) who are aged less than 65 years are at a low risk and should be treated with aspirin or receive no
treatment. Patients over 65 years without other risk factors may be considered at moderate risk and therapy could include warfarin or aspirin. The dose of aspirin should be 300 mg/day, because this dosage has been shown to be effective in patients with AF.

For patients over 75 years of age, a lower INR of 2.0 (1.6-2.5) may be target to minimize bleeding. However, the benefit of this lower warfarin level has not been established, and many scientists disregard age and accept a higher INR target of 2.5.

Recommendations
1. Long-term oral anticoagulation therapy (target INR 2.5; range 2.0- 3.0) should be considered for all AF patients who are at high risk for stroke (level I).
2. Patients aged less than 65 years with no cardiovascular disease or patients who are unable to receive anticoagulants should be offered aspirin 300 mg per day (level I).
3. Although not yet established by randomised studies, patients over 65 years of age without risk factors could be offered anticoagulation or aspirin 300 mg/day (level III).
4. Although not yet established by randomized studies, in patients over 75 years of age, warfarin may be used with a lower INR (target INR of 2.0; range 1.6-2.5) to decrease the risk of hemorrhage (level III).

Carotid Surgery for Asymptomatic Stenosis
The results of trials assessing carotid endarterectomy (CEA) in asymptomatic patients are still a matter of controversy. The largest of these trials, the Asymptomatic Carotid Atherosclerosis Study (ACAS), reported that patients with an asymptomatic carotid stenosis greater than 60% had a 5-year relative risk reduction of 53% of ipsilateral stroke if CEA was performed (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS) 1995). However, the absolute risk reduction was small (5.9% in 5 years), as was the rate of ipsilateral stroke in the medically treated group (11.0% in five years, or 2.3% annually). Moreover, these results were achieved with a perioperative rate of complications (stroke or death) of only 2.3%. Finally, the 5-year results were calculated on the basis of a two follow-ups and extrapolated, which reduces largely the reliability of the effect size.

Recommendations
1. Surgery for asymptomatic carotid stenosis is not generally recommended (level II). It may be discussed on individual patient basis.
Secondary Prevention

Antithrombotic drugs

Aspirin
Aspirin is the best-studied medical therapy used for stroke prevention. The Antiplatelet Trialists' Collaboration performed a meta-analysis of 145 trials, involving 51,144 patients allocated to antiplatelet therapy. They showed a 25% risk reduction of stroke in patients receiving aspirin (Antiplatelet Trialists Collaboration 1994). The optimal dose of aspirin is still a matter of debate. It was suggested that low doses (<160 mg) should be even more effective than medium (160-325 mg) or high (500-1500 mg) doses, since the production of prostacyclin by the vessel walls may be partially preserved (Salt Collaborative Group 1991). However, studies directly comparing the effects of different doses of aspirin failed to show differences in stroke recurrence between low and medium doses (Dutch TIA Trial Study Group 1991) or medium and high doses (UK-TIA Study Group 1991). According to the Antiplatelet Trialists' Collaboration, doses between 160 and 325 mg/day are the most widely tested antiplatelet regimens and may be the most beneficial. However, evidence exists that doses of 50mg daily are also effective (Diener et al. 1996).

Clopidogrel
Clopidogrel is a new thienopyridine derivative, chemically related to ticlopidine. The CAPRIE study, which compared the effects of 75 mg of clopidogrel and 325 mg of aspirin once daily in reducing the composite endpoint of ischemic stroke, MI, or vascular death in 19,185 patients showed a significant absolute risk reduction of 0.5% and a relative risk reduction of 8.7% in favour of clopidogrel (CAPRIE Steering Committee 1996). Clopidogrel is slightly, but significantly more effective as medium-dose aspirin. It is the agent of choice in patients with contraindications, or adverse effects, to aspirin, and may be more effective in higher risk patients and after coronary surgery (Bhatt et al 2000).

Dipyridamole plus Aspirin
The European Stroke Prevention Study (ESPS II) compared aspirin alone (50 mg daily), dipyridamole alone (400 mg daily), aspirin plus dipyridamole, and placebo in the secondary prevention of stroke (Diener et al 1996). The risk reduction of stroke in the aspirin plus dipyridamole group (37.0%) was significantly higher than in either the aspirin group (18.1%) or the dipyridamole group (16.3%). This study was viewed with some criticism previous small trials had showed no benefit of the combination of
dipyridamole and aspirin. Nevertheless, the results of the adequately powered study clearly demonstrate the superiority of the combination treatment against aspirin.

Recommendations
1. Low- or medium-dose ASA (50-325 mg) should be given as first choice agent to reduce stroke recurrence (level I). Where available, the combination of ASA (25mg) and dipyridamol (200mg) twice daily may be given as first choice (level I).
2. Clopidogrel is slightly more effective than aspirin for the prevention of atherothrombotic events (level I). It may be prescribed as first choice or when aspirin is not tolerated or efficacious, and in special situations, such as high-risk patients or a previous event on aspirin (level III).
3. Patients starting treatment with thienopyridine derivatives should receive clopidogrel instead of ticlopidine because it has fewer side-effects (level I); patients who have already been receiving ticlopidine for a long time should be maintained on this regimen because the most severe side-effects (neutropenia and rash) appear at the beginning of treatment.
4. Patients who do not tolerate both ASA or clopidogrel may be treated with dipyridamol ret., 2x200mg daily (level I).

Anticoagulation after Cardio-Embolic Stroke
Oral anticoagulation (INR 2.0-3.0) reduces the risk of recurrent stroke in patients with AF and recent ischaemic stroke (European Atrial Fibrillation Study Group 1995). Oral anticoagulation therapy should also be considered for the many well-established potential causes of embolism. Although evidence from randomised trials is lacking, long-term anticoagulants are routinely used in patients with mechanical prosthetic valves. In this setting, a higher target of an INR (between 3.0 and 4.0) is recommended (Cannegieter et al 1995). Long-term anticoagulation with an INR of 2-3 in patients with rheumatic valvular heart disease, MI, heart failure, cardiomyopathy, arrhythmia other than AF, or PFO may be indicated.

Recommendations
1. Oral anticoagulation (INR 2.0-3.0) is indicated after stroke associated with AF (level I).
2. Patients with mechanical prosthetic valves should receive long-term anticoagulation therapy with a target INR between 3.0 and 4.0 (level III).
3. Patients with proven cardioembolic stroke should be anticoagulated if the risk of recurrence is high with a target INR between 2.0 and 3.0 (level III).
Treatment of hypertension after stroke
The results of the recently published PROGRESS-Trial (2001) indicate that antihypertensive treatment with the ACE-inhibitor perindopril with or without co-treatment with indapamide effectively reduces stroke recurrence rates by 28%. The effect is seen in hypertensive and non-hypertensive patients. A subgroup in the HOPE trial also showed a benefit from antihypertensive treatment after stroke (HOPE, 2000).

Surgery

Carotid Endarterectomy
The North American Symptomatic Carotid Endarterectomy Trial Collaboration (NASCET) (1991) and the European Carotid Surgery Trial (ECST) (European Carotid Surgery Trialists Collaborative Group 1991) established that surgery is efficacious for symptomatic patients with ipsilateral carotid stenosis greater >70%. Although these trials used different methods to measure stenosis, it is possible to predict the percentage of stenosis from one method to another, and there is little difference in their ability to predict ipsilateral stroke.

In the NASCET, patients who underwent CEA had an absolute reduction of 17% in the risk of ipsilateral stroke at 2 years. The authors therefore warn that, if perioperative complications exceed 2.1%, the benefit of CEA will diminish, and, if the complication rate approaches 10%, the benefit will vanish entirely. Although the rate of perioperative complications in the ECST was higher (7.5% of deaths, disabling stroke, or any stroke producing symptoms for more >7 days), surgery-allocated patients still had an significant absolute risk reduction of 6.5% in ipsilateral stroke and a relative reduction of 39%.

The recent NASCET analysis of surgery for symptomatic patients with less than 70% stenosis revealed an absolute risk reduction of 6.5% and a relative risk reduction of 29% for patients with 50-69% stenosis allocated for surgery (Barnett et al 1998).

Angioplasty
Percutaneous transluminal angioplasty (PTA) is a potentially valuable technique. Its advantages over CEA are short hospital stays, the avoidance of general anaesthesia and surgical incision, and the ability to treat surgically inaccessible sites, such as the high cervical internal carotid artery. Moreover, carotid PTA and stenting may be the most effective means of treating restenosis after initial CEA (Yadav et al 1996). However, the main problem of the procedure is that data for the long-term follow-up are not available in a direct comparison with CEA in the CAVATAS trial, both CE and
PTA were equally effective. Several randomised trials (CREST, SPACE, ICSS, EVA-2S) are underway. In the meantime, PTA may be considered as an experimental alternative to CEA. The results of CAVATAS, the first randomised comparison of angioplasty and CEA have been communicated in several conferences, but are not published yet. The results so far indicate that both intervention seem to have comparable procedural risks (CAVATAS 2001).

Recommendations
1. CEA is indicated for symptomatic patients with stenosis of 70-99%, this is valid only for centres with a perioperative complication rate (all strokes and death) less <6% (level I).
2. CEA may be indicated for some patients with stenosis of 50-69% without a severe neurologic deficit; this is valid only for centres with a perioperative complication rate (all strokes and death) less <6%; males with recent hemispheric symptoms are the subgroup of patients most likely to benefit from surgery (level I).
3. CEA is not recommended for patients with stenosis less <50% (level I).
4. CEA should not be performed in centres not exhibiting equally low complication rates like NASCET or ECST.
5. CEA may be indicated for some patients with asymptomatic stenosis of 60 and 99%; only patients with a low surgical risk (<3%) and a life expectancy of at least 5 years are likely to benefit from surgery (level II).
6. Carotid PTA with or without stenting may be performed for patients with contra-indications to CEA (level IV).
7. Carotid PTA with or without stenting may be indicated for patients with stenosis at surgically inaccessible sites (level IV).
8. Carotid PTA and stenting may be indicated for patients with re-estenosis after initial CEA (level IV).

Appendix
EUSI Members:
Markku Kaste, Helsinki, Finland (Chairman), nominated by ESC
Julien Bogousslavsky, Lausanne, Switzerland representing the ENS
Otto Busse, Minden, Germany, representing the ESC
Michael Brainin, Maria Gugging, Austria, representing the EFNS
Hubert Kwiecinski, Warszawa, Poland, representing the ENS
Tom Skyhoj Olsen, Copenhagen, Denmark, representing the EFNS
Jean-Marc Orgogozo, Bordeaux, France, representing the ESC
Werner Hacke, Heidelberg, Germany (Secretary)
This paper is approved and endorsed by the EFNS, ENS and ESC
References

Abbott R, Yin Y, Reed D, Yano K
Risk of stroke in male cigarette smokers

Aboderin I, Venables G, For the PAN European Consensus Meeting on Stroke Management
Stroke management in Europe
Journal of Internal Medicine 1996; 240: 173-180

Guidelines for the Management of Patients with Acute Ischemic Stroke. A Statement for Healthcare Professionals from a Special Writing Group of the Stroke Council, American Heart Association
Stroke 1994; 25(9): 1901-1914

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
BMJ 1994; 308: 81-106

Asplund K, Marké L-Å, Terént A, Gustafsson C, Wester P
Costs and gains in stroke prevention: European perspective
Cerebrovasc Dis 1993; 3(suppl 1): 34-42

Benefit of endarterectomy in patients with symptomatic moderate or severe stenosis

Superiority of clipidogrel versus aspirin in patients with prior cardiac surgery
Circulation 2001; 103: 363-368

Guidelines for carotid endarterectomy. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association
Stroke 1998; 97: 501-509

Blaw G, Lagaay A, Smelt A, Westendorp R
Stroke, statins and cholesterol: a meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors
Stroke 1997; 28: 946-950

Brainin M, European Federation of Neurological Societies Task Force
Neurological acute stroke care: the role of European neurology
European Journal of Neurology 1997; 4: 435-441
Brandt T, von Kummer R, Müller-Küppers M, Hacke W  
Thrombolytic Therapy of Acute Basilar Artery Occlusion: Variables Affecting Recanalization and Outcome  
Stroke 1996; 27(5): 875-881

Brott T, Reed RL  
Intensive care for acute stroke in the community hospital setting.  
Stroke 1989; 20: 694-697

Brott T, Fieschi C, Hacke W  
General therapy of acute ischemic stroke.  
In: Hacke W, Hanley DF, Einhäup K, Bleck TP (eds): NeuroCritical Care  
Berlin, Springer 1994; 553-577

Cannegieter S, Rosendaal F, Witzen A, Van Der Meer F, Vandenbroucke J, Briët E  
Optimal oral anticoagulation therapy in patients with mechanical heart valves  
N Eng J Med 1995; 333: 11-17

CAPRIE Steering Committee  
A randomised, blinded trial of dospidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)  
Lancet 1996; 348: 1329-1339


Castillo J, Dávalos A, Marrugat J, Noya M  
Timing for fever-related brain damage in acute ischemic stroke  
Stroke 1998; 29: 2455-2460

CAVATAS Investigators  
Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertrebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial  
Lancet 2001; 357: 1729-1737

Chamorro A, Vila N, Asaco c, Blanc R  
Heparin in stroke with atrial fibrillation  
Arch Neurol 1999; 56: 1098-1102

Cigarette smoking and risk of stroke in middle-aged woman  

Blood pressure, stroke, and coronary heart disease, part 2: short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context  
Lancet 1990; 335: 827-838
Diener H, Cunha L, Forbes C, Silvenius J, Smets P, Lowenthal A
European stroke prevention study 2, dipyridamole and acetylsalicylic acid in
the secondary prevention of stroke

Diringer M, Ladenson P, Stern B, Schleimer J, Hanley D
Plasma atrial natriuretic factor and subarachnoid hemorrhage
Stroke 1998; 19: 1119-1124

Dutch TIA Trial Study Group: A comparison of two doses of aspirin (30 mg vs
283 mg a day) in patients after a transient ischemic attack or a minor ischemic
stroke

Einhäupl K, Diener C, Hacke W, Hennerici M, Ringelstein B
Behandlung des akuten ischämischen Insults
Dt. Ärzteblatt 1999; 325: 1123-1130

European Ad Hoc Consensus Group: European strategies for early
intervention in stroke
Cerebrovasc Dis 1996; 6: 315-324

European Atrial Fibrillation Study Group: Optimal oral anticoagulation therapy
with nonrheumatic atrial fibrillation and recent cerebral ischemia

European Carotid Surgery Trialists’ Collaborative Group
MRC European Carotid Surgery Trial: Interim results for symptomatic patients
with severe (70-99%) or with mild (0-29%) carotid stenosis
Lancet 1991; 337: 1235-1243

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study
(ACAS)
Endarterectomy for asymptomatic carotid artery stenosis
JAMA 1995; 273: 1421-1428

Guidelines for the management of transient ischemic attacks. From the Ad
Hoc committee on guidelines for the management of transient ischemic attacks
of the American Heart Association
Stroke 1994; 89: 2950-2965

Fogelholm R, Rissanen A, Nenonen
Direct and indirect costs incurred by cerebrovascular diseases in Finland
Fin med J 2001; 56: 3563-3567

Forbes J
Cost of stroke
Scott Med J 1993; 38 (suppl): 1-4
Furlan A
The heart and stroke
New York, Springer 1987

Furlan A, Higashida R, Wechsler L, Schulz G, II P
PROACT II: Recombinant prourokinase (r-ProUK) in Acute Cerebral
Thromboembolism
Initial Trial Results The PROACT II Investigators
Stroke 1999; 30: 234

et al
Prevention of first stroke. A review of guidelines and a multidisciplinary
consensus statement from the National Stroke Association
JAMA 1999; 281: 1112-1120

Grau A, Buggle F, Heindl S, Steichen-Wiehn C, Banerjee T, Maiwald M,
Rohlf M, et al.
Recent infection as a risk factor for cerebrovascular ischemia
Stroke 1995; 26: 373-379

Grotta J, Pasteur W, Khwaja G, Hamel T, Hamel T, Fisher M, Ramirez A
Elective intubation for neurologic deterioration after stroke
Neurology 1995; 45: 640-644

Hacke W, Zeumer H, Ferbert A, Brückmann H, Del Zoppo G
Intra-arterial thrombolytic therapy improves outcome in patients with acute
vertebrobasilar occlusive disease
Stroke 1988; 19: 1216-1222

Hacke W, Stingele R, Steiner T, Schuchardt V, Schwab S
Critical care of acute ischemic stroke
Intensive Care Med 1995; 21: 856-862

Hacke W, Schwab S, Horn M, Spranger M, DeGeorgia M, von Kummer R
Malignant middle cerebral artery territory infarction: Clinical course and
prognostic signs
Arch Neurol 1996; 53: 309-315

V, et al
Randomised double-blind placebo-controlled trial of thrombolytic therapy with
intravenous alteplase in acute ischaemic stroke (ECASS II)
The Lancet 1998; 352: 1245-1251

Hart R, Sherman D, Easton D, Cairns J
Prevention of stroke in patients with nonvalvular atrial fibrillation:
views and reviews
Neurology 1998; 51: 674-681
The Hemodilution in Stroke Study Group: Hypervolemic hemodilution treatment of acute stroke. Results of a randomized multicenter trial using pentastarch
Stroke 1989; 20: 317-323

Heros R
Surgical treatment of cerebellar infarction
Stroke 1992; 23: 937-938

Hillbom M, Kaste M
Does ethano intoxication promote brain infarction in young adults?
Lancet 1978; 2: 1181-1183

Hillbom M, Kaste M
Alcohol intoxication: A risk factor for primary subarachnoid hemorrhage
Neurology 1982; 32 (7): 706-711

The HOPE Investigators: Effects of an ACE inhibitor, ramipril, on cardiovascular events in high-risk patients
NEJM 2000; 342-14-153

Horner J, MAsséy EW
Silent aspiration following stroke
Neurology 1988; 38: 317-319

Indredavik B, Slørdahl S, Bakke F, Roksetz R, Hāheim L
Stroke unit treatment: long-term effects
Stroke 1997; 28: 1861-1866

International Stroke Trial Collaborative Group
The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneousheparin, both, or neither among 19435 patients with acute ischaemic stroke
The Lancet 1997; 349: 1569-1581

Isard P, Forbes J
The cost of stroke to the National Health Service in Scotland
Cerebrovasc Dis 1992; 2: 47-50

Italian Acute Stroke Study Group: Haemodilution in acute stroke: Results of the Italian haemodilution trial
Lancet 1988; 8581: 318-321

Kaste M, Somer H, Konttinen A
Heart type creatine kinase isoenzyme (CK MB) in acute cerebral disorders
British Heart Journal 1978; 40: 802-805

Kothari R, Hall K, Brott T, Broderick J
Early Stroke Recognition: Developing an Out-of-Hospital NIH Stroke Scale
Acad Emerg Med 1997; 4(10): 986-990
Acute Stroke: Usefulness of Early CT Findings before Thrombolytic Therapy
Radiology 1997; 205: 327-333

Langhorne P, Williams B, Gilchrist B
Do stroke units safe lifes?
Lancet 1993; 342: 395-398

Antithrombotic therapy in atrial fibrillation
Chest 1998; 114(5): 579-589

Lee I, Hennekens C, Berger K, Buring J, Manson J
Exercise and risk of stroke in male physicians
Stroke 1999; 30: 1-6

The long-term intervention with paravastatin in ischemic disease (LIPID) Study
Group, Prevention of cardiovascular events and death with paravastatin in
patients with coronary heart disease and a broad range of initial cholesterol
levels

A prospective study of aspirin use and primary prevention of cardiovascular
disease in women
JAMA 1991; 266: 521-527

Multicenter Acute Stroke Trial – Europe Study Group:
Thrombolytic therapy with streptokinase in acute ischaemic stroke

Multicenter Acute Stroke Trial – Italy (MAST-I) Group
Randomised controlled trial of streptokinase, aspirin, and combination of both
in treatment of acute ischaemic stroke
Lancet 1995; 46: 1509-1514

National Institute of Neurologic Disorders and Stroke:
rt-PA Stroke Study Group (NIHDS):
Tissue plasminogen activator for acute ischemic stroke

Norris J
Effects of cerebrovascular lesions on the heart
Neurol Clin 1983; 1: 87-101

North American Symptomatic Carotid Endarterectomy Trial Collaborators
(NASCET)
Beneficial effect of carotid endarterectomy in symptomatic patients with high-
grade carotid stenosis
Pan European Consensus Meeting on Stroke management, Helsingborg, Sweden, 8-10 November 1995 (abstracts)
Neurol Neurochir Pol 1997; 31 (1 Suppl 1): 1-40

Randomised trial of prophylactic daily aspirin in British male doctors
BMJ 1988; 296: 313-316

Plehn J, Davis B, Sacks F, Rouleau J, Pfeffer M, Bernstein V, al e
Reduction of stroke incidence after myocardial infarction with pravastatin: the cholesterol and recurrent events (CARE) study
Circulation 1999; 99: 216-233

PROGRESS Collaborative Group
Randomized trial of a perindobril-based blood pressure lowering regiment among 6105 individuals with previous stroke or transient ischaemic attack
Lancet 2001; 358 (9287) 1033-1041

Prospective Studies Collaboration
Cholesterol, diastolic blood pressure and stroke
13,000 strokes in 450,000 people in 45 prospective cohorts
Lancet 1995; 346: 1647-1653

Pulsinelli W, Levy D, Sigsbee B, Scherer P, Plum F
Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus

Reith J, Jørgensen H, Pedersen P, Nakayama H, Raaschou H, Jeppesen L, Olsen T
Body temperature in acute stroke: relation to stroke severity, infarct size, mortality and outcome
Lancet 1996; 347: 422-425

Therapeutic strategies in space-occupying cerebellar infarction based on clinical, neuroradiological and neurophysiological data
Cerebrovasc Dis 1993; 3: 45-55

Decompressive surgery in space-occupying hemispheric infarction: Results of an open, prospective trial
Crit Care Med 1996; 23(9): 1576-1587

Ringleb, PA, Bertram M, Keller E, Hacke W
Hypertension in patients with cerebrovascular accident: To treat or not to treat?
Rännig O, Guldvog B
Stroke units versus general medical wards. I. Twelve and eighteen-month survival. A randomized, controlled trial

The protective effect of moderate alcohol consumption on ischemic stroke
JAMA 1999; 281: 53-60

Saito I, Segawa H, Shiozawa Y, Taniguchi M, Tsutsumi K
Middle cerebral artery occlusion: Correlation of computed tomography and angiography with clinical outcome
Stroke 1987; 18: 863-868

Scandinavian Stroke Study Group
Multicenter trial of hemodilution in acute ischemic stroke
I. Results in the total patient population
Stroke 1987; 18: 691-699

SALT Collaborative Group
Swedish aspirin low-dose trial (SALT) of 75mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events
Lancet 1991; 228: 1345-1349

Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W
Moderate Hypothermia in the Treatment of Patients With Severe Middle Cerebral Artery Infarction
Stroke 1998; 29(12): 2461-2466

SHEP Cooperative Research Group
Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP)
JAMA 1991; 365: 3255-3264

Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia

Sherman D, for the STAT Writers Group
Defibrinogenation with Viprinex TM (Ancrod) for the Treatment of Acute, Ischemic Stroke
Stroke 1999; 30(1): 234

Steering Committee of the Physicians’ Health Study Research Group
Final report of the ongoing physicians health study
Steiner T, Mendoza G, De Georgia M, Schellinger P, Holle R, Hacke W
Prognosis of stroke patients requiring mechanical ventilation in a neurological critical care unit
Stroke 1997; 28(4): 711 – 715

Stand T
Evaluation of long-term outcome and safety after hemodilution therapy in acute ischemic stroke
Stroke 1992; 23: 657-662

Stroke Units Trialists’ Collaboration
A systematic review of the randomised trials of organised impatient (stroke unit) care after stroke
Br Med J 1997; 314: 1151-1159

Swanson R
Intravenous heparin for acute stroke
What can we learn from the megatrials?
Neurology 1999; 52: 1746-1750

UK Prospective Diabetes Study (UKPDS) Group
Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk complications in patients with type 2 diabetes (UKPDS 33)
Lancet 1998; 352: 837-853

UK-TIA Study Group
The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results
J Neurol Neurosurg Psychiatry 1991; 54: 1044-1054

WHO Task Force on Stroke and Other Cerebrovascular Disorders
Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and Other Cerebrovascular Disorders
Stroke 1989; 20: 1407-1431

Yadav J, Roubin G, King P, Iyer S, Vitek J
Angioplasty and stenting for restenosis after carotid endarterectomy, initial experience
Stroke 1996; 27: 2075-2079
Table 1  
Definitions for levels of evidence  
(modified from Adams et al 1994)

**Level I: highest level of evidence**  
*Source:*  
a. Primary endpoint from randomized, double-blind study with adequate sample size  
b. Properly performed meta-analysis of qualitatively outstanding randomized trials

**Level II: intermediate level of evidence**  
*Source:*  
a. Randomized, non-blinded studies  
b. Small randomized trials  
c. Pre-defined secondary endpoints of large randomized trials

**Level III: lower-level of evidence**  
*Source:*  
a. Prospective case series with concurrent or historical control post hoc analyses of randomized trials

**Level IV: undetermined level of evidence**  
*Source:*  
a. Small case series without control, case reports  
b. General agreement despite of lack of scientific evidence from controlled trials
Table 2  
Suggested antihypertensive treatment in acute ischemic stroke (first 24-48 h)  
(modified from Brott et al 1994 and Ringleb et al 1998)  
(availability of substances may vary between countries)

1) Systolic BP 180-220 mm Hg and/or  
   Diastolic BP 105-120 mm Hg  
   do not treat

2) Systolic BP > 220 mm Hg on repeated measures,  
   diastolic BP 120-140 mm Hg, or both  
   Orally  
     Captopril 6.25-12.5 mg  
   Parenterally  
     Labetalol 5-20 mg i.v.  
     Urapidil 10-50 mg i.v., followed by 4-8 mg/h i.v.  
     Clonidin 0.15-0.3 mg i.v. or s.c.  
     Dihydralazin 5 mg i.v. plus metropolol 10 mg i.v.

3) Diastolic BP > 140  
   Nitroglycerin 5 mg i.v., followed by 1-4 mg/h i.v.  
   Sodium nitroprusside 1-2 mg (rarely given)

\[a\] Avoid labetalol in patients with asthma, cardiac failure, severe conduction abnormalities, and bradycardia

\[b\] In patients with unstable conditions and rapidly fluctuating blood pressure alternating Urapidil/Arterenol treatment may be used
### Table 3
**Remaining indications for heparin treatment after ischemic stroke**

- Stroke due to cardiac emboli with high risk of re-embolisation (artificial valves, AF, MI with mural thrombi, left atrial thrombosis)
- Coagulopathies such as protein C and S deficiency, activated protein C-resistance
- Symptomatic dissection of extracranial arteries
- Symptomatic extra- and intracranial stenoses
  - Symptomatic internal carotid stenosis prior to operation
  - Crescendo transient ischaemic attacks or stroke in progression
  - Venous sinus Thrombosis
The European Stroke Initiative (EUSI)

Members:
Markku Kaste, Helsinki FIN (Chairman)

Julien Bogousslavsky, Lausanne SUI, representing the ENS
Otto Busse, Minden GER, representing the ESC
Eberhard Deisenhammer, Linz AUS, representing the EFNS
Hubert Kwiecinski, Warsaw POL, representing the ENS
Tom Skyhoj Olsen, Copenhagen DEN, representing the EFNS
Jean-Marc Orgogozo, Bordeaux FRA, representing the ESC

Werner Hacke, Heidelberg GER (Secretary)

This paper is approved and endorsed by
- The European Federation of Neurological Societies (EFNS)
- The European Neurological Society (ENS)
- The European Stroke Council (ESC)