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CROATIAN SOCIETY FOR NEUROVASCULAR DISORDERS OF CROATIAN MEDICAL ASSOCIATION
CROATIAN STROKE SOCIETY

REFERENCE CENTER FOR NEUROVASCULAR DISORDERS OF CROATIAN MINISTRY OF HEALTH

UNIVERSITY DEPARTMENT OF NEUROLOGY, SESTRE MILOSRDNICE UNIVERSITY HOSPITAL, ZAGREB

RECOMMENDATIONS FOR STROKE MANAGEMENT 2006 UPDATE

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SUMMARY – This article brings an update of the Recommendations for Stroke Management, first published in this journal in 2001. The Recommendations are consistent with the Recommendations of three European societies represented in the European Stroke Initiative: the European Stroke Council, the European Neurological Society, and the European Federation of Neurological Societies, and are in concordance with the Guidelines of the American Heart Association/American Stroke Association Council on Stroke, approved by the American Academy of Neurology. The Recommendations have been endorsed by the Croatian Society for Neurovascular Disorders of Croatian Medical Association, Croatian Stroke Society, and University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Croatian Ministry of Health.

Key words: *Stroke; Cerebrovascular disorders; Stroke therapy; Guidelines; Thrombolytic therapy; Stroke units*

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Introduction

Acute stroke is one of the leading causes of morbidity and mortality worldwide. In industrialized countries, stroke ranks either second or third most common cause of death. In Europe, the crude death rate ranges from 63.5/100,000 in males in Switzerland to 273.4/100,000 in females in Russia[1-3]. A decrease in the stroke incidence and lower stroke mortality in western, industrialized countries are the result of preventive actions taken in the 1950s with lifestyle modification and risk factor control[4]. During that time, Croatia as a part of Yugoslavia, was in the group of East European countries, with an increase in the stroke incidence and mortality[5]. During the last decade, Croatia has become an independent state, first faced with the war, population migration and lifestyle changes, which led to an increase in the rate of stroke victims[6,7]. During the last few years, stroke ranked the second leading cause of death in both sexes in Croatia[8], yet the implementation of new concepts of stroke management and treatment[9-13] has led to better recognition of stroke victims, resulting in a higher stroke incidence[14] and lower stroke mortality, thus increasing the stroke burden. Although great efforts have been invested in public campaigns through mass media[15], improvement of the quality of studies to provide appropriate education for healthcare professionals and health related professionals is needed[16]. Therefore, the Croatian Society for Neurovascular Disorders of the Croatian Medical Association, Croatian Stroke Society, and University Department of Neurology, Sestre milosrdnice University Hospital as Reference Center for Neurovascular Disorders of the Croatian Ministry of Health, took an active part in these endeavors by publishing guidelines for stroke prevention and management[10-13], as well as on the management of headache[17] and on brain death[18] as the possible causes, symptoms or consequences of stroke. Now, the same expert group have published guidelines consistent with the EUSI (European Stroke Initiative) guidelines on ischemic[19-21] and hemorrhagic[22] stroke management, which are in accordance with the European Neurological Society, European Federation of Neurological Society and European Stroke Council representing European Stroke Conference, as well as with other published North American stroke guidelines[23,24], based on data obtained from clinical trials, to provide updated recommendations that can be used on adopting new treatment concepts, therapeutic methods and procedures[25].

On developing the present guidelines, the panel applied the Rules of Evidence[26] and formulation of strength to set the recommendations, as in the previous recommendations (Table 1).

PART I
ORGANIZATION OF STROKE CARE

The firm scientific basis for organized stroke care is relatively short, dating back by only a little more than a decade. The existing knowledge extending into several areas with important implications for clinical practice is identified as: education, organization of pre-hospital services, hospital treatment, and follow-up care. It differs around the world based on local practices and dif-

Level I: high level of evidence	Source A: primary endpoint from randomized, double-blind study with sufficient sample size Source B: properly performed meta-analysis of qualitatively outstanding randomized trials
Level II: intermediate level of evidence	Source A : randomized, non-blind studies Source B: small randomized trials Source C: predefined secondary endpoints of large randomized trials
Level III: low level of evidence	Source A: a prospective case series with concurrent or historical control Source B: post-hoc analyses of randomized trials
Level IV: undetermined level of evidence	Source A: small case series without control, case reports Source B: general agreement despite the lack of scientific evidence from controlled trials

Table 1. Definitions of the levels of evidence and classes of recommendations used in the article

ferences in health care systems and resources, and must be taken into account on health care system restructuring, which is under way in Croatia. Overall, more progress is evident in hospital care, primarily in the formation and promotion of "stroke units".

Education

Many patients and relatives do not recognize the symptoms of stroke and do not realize that seeking treatment is urgent. Reasons for this shortcoming include poor awareness of stroke signs by the victim or family with inappropriately planned action on seeking immediate medical help, and not perceiving stroke as an emergency by medical personnel[15,27-29]. These facts emphasize the need for continuous education, especially through mass media campaigns. In Croatia, television was the most common source of information on stroke risk factors and signs, and on the action planned[15].

The aims of public education are to enable and encourage the general population to immediately recognize stroke symptoms and signs, to realize the need of urgent medical attention, and to use emergency transportation services to an appropriately equipped hospital. Primary contact with general practitioners may only cause delays.

Professional groups included in stroke patient management include emergency medicine physicians and technicians, other specialists, nurses, and general practitioners. They should also be educated to shorten the time from stroke onset to an adequately equipped unit. The medical personnel should be trained in recognizing the acute presentations of ischemic stroke (Table 2), and should be able to cope with the early complications after a stroke has occurred. Training should include the ability to conduct medical examination focused on the level of consciousness, presence of focal weakness, presence of seizure activity, and recognition of aphasia and other major cognitive disturbances. The need of the accompanying person to estimate the exact time of stroke onset and course should be understood. The early assessment of stroke victims should be started to estimate other life-threatening concomitant diseases and to exclude other conditions mimicking stroke.

Referral

Stroke is a medical and occasionally also a surgical emergency. The majority of stroke patients do not receive appropriate therapy because they do not reach the hospital soon enough[30,31]. Successful care of the acute stroke victim as an emergency depends on a chain of rapid recognition of stroke warning signs and appropriate response to them, immediate use of emergency medical system (EMS) services, priority transport with notification of the receiving hospital, and rapid and accurate diagnosis and treatment at the hospital. Ambulance transportation decreases the delay in arrival to the hospital after stroke onset (Level III). The EMS system should have an electronic validated algorithm of questions to diagnose stroke during the phone interview and identify and to provide appropriate help for patients

Table. 2. Common patterns of neurological impairments in patients with acute ischemic stroke

Area involved	Symptoms
Left (dominant) hemisphere – major or branch cortical infarction	Aphasia Right hemiparesis Right-sided sensory loss Right-sided spatial neglect Right homonymous hemianopia Impaired right conjugate gaze
Right (nondominant) hemisphere – major or branch cortical infarction	Left hemiparesis Left-sided sensory loss Left-sided spatial neglect Left homonymous hemianopia Impaired left conjugate gaze
Deep (subcortical) hemisphere or brain stem	Hemiparesis (pure motor stroke) or sensory loss (pure sensory stroke) Dysarthria, including dysarthria-clumsy hand Ataxia-hemiparesis No abnormalities of cognition, language, or vision
Brain stem	Motor or sensory loss in all four limbs Cross signs (signs on the same side of face and other side of body) Dysconjugate gaze Nystagmus Ataxia Dysarthria Dysphagia
Cerebellum	Ipsilateral limb ataxia Gait ataxia

who need emergency care[32]. The priority in evaluation and transportation by EMS should be given to patients with the onset of stroke symptoms within less than 3 h, victims with impaired consciousness, seizures, vomiting, hemodynamic instability, or other early complications or comorbidity of stroke. Therefore, the initial assessment should include the "ABC" observation: airways, breathing and circulation. If the airways are impaired, the placement of endotracheal tube should be considered. Determination of arterial oxygen saturation using infrared pulse oxymetry should be performed and the patient should be treated with supplemental oxygen at 2-4 liter *per* minute *via* nasal tube if necessary. If hypotension is present, volume depletion is usually the cause, and i.v. infusion should be started. Acute stroke leads to a hypertensive reaction and most investigators nowadays agree that hypertension should not be treated drastically in the first hours, and antihypertensive drugs should only be used in rare cases in the early hours following acute ischemic stroke. Sublingual nifedipine should be avoided.

If a general practitioner or other doctor receives a call or consults a patient with suspected stroke, he or she should recommend and arrange emergency transportation, preferably through EMS, to the nearest emergency room of a hospital providing organized acute stroke care or with a stroke unit if available. The EMS ambulance dispatchers should inform the stroke unit personnel that they are going to refer a stroke patient and describe the clinical status.

Stroke units

Stroke patients should be treated in stroke unit[10-12,33-36], since recent studies have supported the effectiveness of stroke units and management in a stroke rehabilitation unit confers survival benefits 10 years after stroke, probably because long-term survival is related to early reduction in disability[35]. An estimate based on data obtained from the North East Melbourne Stroke Incidence Study showed that although t-PA was the most potent intervention, the management in stroke units had the greatest population benefit[36]. Stroke unit care, as provided in routine clinical practice in United Kingdom[37] and Sweden[38-40], is associated with reduced case fatality by up to 25%, and reduction in mortality by 46% compared with general ward treatment[41]. A meta-analysis by the Stroke Unit Trialists' Collaboration also showed a reduction in death or dependence and a reduction in death or need of institutional care when treated in a stroke unit in comparison with a general medical ward (Level I). The absolute changes indicated a 3% reduction in all cause mortality (NNT 33), a 3% reduction in the need of nursing home care, and a 6% increase in the number of independent survivors (NNT 16). 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.

A stroke unit is established as a hospital unit or part of a hospital unit that exclusively or nearly exclusively takes care of stroke patients. There are various forms of stroke unit care[19], having in common that they all provide a coordinated multidisciplinary approach to treatment and care. The core disciplines of such a team are: medicine, nursing, physiotherapy, occupational therapy, speech and language therapy, and social work. The primary goal of such a multidisciplinary team is the interest in stroke management and work in a coordinated way through regular meetings and planning patient care. Programs of regular staff education and training should be provided.

The typical components of care in the stroke unit trials[42] were as follows: (1) medical assessment and diagnosis including computerized tomography (CT) scanning, early assessment of nursing and therapy needs; (2) early mobilization, prevention of complications, treatment of hypoxia, hyperglycemia, pyrexia and dehydration; and (3) rehabilitation policies (coordinated multidisciplinary team care, early assessment of needs after discharge).

Stroke units are described in several categories:

1) acute stroke unit admitting patients for acute and continuing treatment for several days but usually less than 1 week;
2) comprehensive stroke unit admitting patients for acute and continuing treatment and rehabilitation for several weeks if necessary;
3) 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 established in hospitals where stroke units are not available. It is a mobile team offering stroke care and treatment to stroke patients at a variety of wards.

The Stroke Unit Trialists' Collaboration[43] in a systematic review of 29 clinical trials showed that interdisciplinary stroke rehabilitation therapeutic environment accounted for much of the success of stroke units. The success of stroke units appears to be a consequence of stroke rehabilitation therapies rather than acute intensive medical monitoring, although more research is needed[44]. Comprehensive stroke rehabilitation units are expensive, but mobile stroke teams do not confer the same benefit[45] and have no major impact on death, dependency, or the need of institutional care when compared with care at general wards[46]. The concept becoming increasingly recognized is that the brain is primed to recover early after a stroke and that delays in rehabilitation will reduce the opportunity for maximal neurological recovery[47].

The size of a stroke unit should be adequate to provide specialist multidisciplinary stroke unit care throughout hospital stay. In practice, this is often achieved with a single comprehensive unit (in small hospitals) or a combination of acute unit and rehabilitation units (in larg hospitals). Further evidence is needed to recommend the type and size of the most effective stroke units in more detail. The minimal requirements for centers managing acute stroke patients and additional recommended facilities are listed in Table 4.

The organization of stroke services plays a key role in the provision of effective therapies and in improving the overall outcome after stroke. Despite strong scientific evidence and guidelines support, organized stroke care is still far from implemented, and inequalities in care continue to exist, even locally[48]. According to countries, the reported proportion of patients treated at stroke units ranges from 23% in Australia, 31% in Canada, 50% in the UK to more than 80% in Scandinavian countries[49]. In Japan, <3% of acute hospitals have a dedicated stroke unit[50]. Therefore, the introduction of organized stroke care, adapted to local practice, is urgently needed. Since the specialized treatment is expensive and not available everywhere, a telemedicine stroke network could be established with expertise stroke centers providing 24-hour service for teleconsultation[51].

Recommendations

1. Stroke needs to be considered a medical emergency that requires public education, a referral and treatment network, and fast management.
2. In case that stroke happens, the emergency medical team should be called immediately (Level III). Patients should be transported by the emergency medical team as fast as possible to qualified centers.
3. Stroke patient should be treated in specialized stroke units (Level I).
4. Stroke units should provide coordinated multidisciplinary care by medical, nursing and therapy staff specialized in stroke care (Level I).
5. Patients with subarachnoid hemorrhage should be referred urgently to a center with facilities for neurosurgical treatment, neuroradiological interventions and neurointensive care (Level I).

MANAGEMENT IN THE EMERGENCY ROOM (ER)

The first goal of the initial diagnostic evaluation is to confirm that the patient's impairments are due to stroke and not due to another systemic or neurological disorder. Second, the evaluation helps distinguish between stroke types and determine advisability of acute treatment with approved thrombolytic agents for ischemic stroke or a clinical trial of recombinant factor VII for hemorrhagic stroke. Third, diagnostic studies are carried out to screen for acute medical or neurological complications of stroke. Finally, the evaluation provides history data or other information that can be used to establish the vascular distribution of stroke and to provide clues about its likely pathophysiology and etiology. These data are essential for further rational decisions about prevention of recurrent stroke.

Obtaining history and performing general medical and neurological examinations rapidly provide the foundation for urgent evaluation. The clinical assessment is supplemented with selected diagnostic tests.

The physician must first determine the reason for the patients's neurological impairments. Stroke patients usually present with a history of sudden or rapid onset of focal neurological symptoms. Some patients may have a stepwise or gradual worsening or waxing and waining of symptoms. Most patients are alert, although patients with major hemispheric infarctions, basilar artery occlusion, or cerebellar strokes with edema causing brainstem compression can have a decreased level of consciousness. Headaches occur in approximately 2% of cases. Nausea and vomiting can occur with strokes in the brainstem or cerebellum.

Common patterns of neurological abnormalities in patients with ischemic stroke and corresponding affected brain areas are listed in Table 2. In general, the di-

agnosis of stroke is straightforward. The accuracy (the degree to which the diagnosis agrees with the perceived "standard") of physicians' diagnosis of stroke generally is good. In one study, emergency department physicians correctly identified 152 of 176 consecutive stroke patients (86.4% sensitivity) and 1818 of 1835 patients without stroke (99.1% specificity)[52]. Still, errors in clinical diagnosis can occur. In one series of 821 consecutive patients initially diagnosed with stroke, 13% were later determined to have other conditions[53]. Several conditions mimic stroke (Table 3). Frequent alternative diagnoses include unrecognized seizures, confusional states, syncope, toxic or metabolic disorders, including hypoglycemia, brain tumors, and subdural hematoma. These stroke mimics are commonly, but not always, associated with global rather than focal neurological symptoms and are usually readily detected with standard laboratory tests, listed in Table 5. They can also help in differential diagnosis of coma (Table 6).

Differentiation of ischemic or hemorrhagic stroke is especially important, because of the marked difference in the management of these conditions. Some studies show that features of the history and physical examination can be used to help distinguish hemorrhagic from ischemic strokes, and one study found that the chance of intracranial hemorrhage was more than double with the presence of at least one of the following findings: coma on arrival, vomiting, severe headache, current warfarin therapy, systolic blood pressure >220 mm Hg, or glucose level >170 mg/dL in a nondiabetic patient[54]. The absence of these features decreases the odds of hemorrhage by approximately one third. Scales to differentiate ischemic or hemorrhagic stroke have been developed based on these types of studies. However, diagnostic errors based solely on clinical features still occur and the level of accuracy is insufficient to guide treatment decision. Because clinical findings overlap, a brain imaging study is mandatory to distinguish ischemic stroke from hemorrhage or other structural brain lesions that may imitate stroke[55].

At initial patient evaluation questions to be answered are:

1. Is it a stroke?
2. Is there a life-threatening concomitant disease?
3. What kind of stroke it is?
4. The interval between the onset of symptoms and admission.
5. The presence of increased intracranial pressure (ICP).
6. The presence of a concurrent underlying severe disease.
7. What is the prognosis?

EMERGENCY DIAGNOSTIC TESTS

Time is critical in stroke patients since the therapeutic window may be quite narrow for specific treatment. Upon admission to the ER, diagnostic tests (Table 5) are needed to differentiate between various types of acute stroke (ischemic, brain hemorrhage, subarachnoid hemorrhage (SAH)), or to rule out other brain diseases (Table 3). They are essential to obtain an impression about the underlying cause of stroke (cardiac or carotid disease, risk factors), to provide a basis for physiological monitoring of the stroke patient, and to identify concurrent diseases or involving complications of stroke that may influence prognosis.

Cranial computed tomography (CT)

Emergency, noncontrast-enhanced cranial CT is widely available and can reliably distinguish between hemorrhage and ischemic stroke or subarachnoid hemorrhage, and to rule out other brain diseases (Level I)[56]. It is relatively insensitive in detecting acute and small cortical or subcortical infarctions, especially in the posterior fossa. In most cases, the use of a contrast infusion does not provide additional information and is not necessary unless it is required for CT angiography (and more recently CT perfusion) or there is a concern about a brain tumor or infectious process. Signs of early ischemia can sometimes be detected as early as 2 h after stroke onset, but this may be difficult even for the trained examiner, in particular in very early studies. Early infarct signs include sulcus effacement, swelling of the basal ganglia and the hyperintense middle cerebral artery (MCA) sign, and loss of gray-white differentiation in the cortical ribbon (particularly at the lateral margins of the insula), or the lentiform nucleus. These signs may be detected within 6 hours of onset of symptoms in up to 82% of patients with ischemia in the MCA territory[57,58]. Their presence, associated with poor outcome, is a sign of extensive infarction with intracranial midline shifts indicating a high risk of both secondary hemorrhage (Level I) and large malignant edema formation. The use of scoring systems for early CT changes may improve identification of cerebral ischemia and might provide valuable prognostic information, but are not validated for outcome[59]. For patients who are candidates for treatment

Table 3. Conditions that can cause stroke syndrome (stroke mimics)

Diagnosis	Key features
Fits, with Todd's paresis	Commonest cause for misdiagnosis of recurrent stroke. Clinical diagnosis, usually requiring an eyewitness. Consider ictal features (loss of consciousness, convulsions, tongue biting, incontinence) and postictal features (headache, sleepiness, confusion).
Cerebral tumors, primary or secondary	CT scan diagnosis. There may be features of raised intracranial pressure (headache, vomiting, drowsiness, papilledema). Onset is slower than stroke. A step-wise progression over days or weeks is associated with space-occupying lesions, but only 1 in 6 patients with a progressive course has a tumor. Onset may be sudden if there is bleeding into the tumor.
Hypoglycemia	Almost always drug-induced, severe, hypoglycemia. Usually rapidly reversible, but hemiplegia can persist for 24 h or more.
Subdural hematoma	CT scan diagnosis. If significant, will cause drowsiness. Sometimes headache, confusion, hemiplegia or dysphasia. Features may fluctuate.
Cerebral abscess	CT scan diagnosis. Usually due to spread from sinuses or ear. Onset is subacute, but there are not always prodromal infective symptoms. Headache usual. Later drowsiness, vomiting, delirium and bradycardia. Dysphasia, visual field defects and facial weakness more common than hemiplegia. Avoid lumbar puncture. Needs surgical drainage. 25% mortality, even if optimally treated.
Encephalitis	May sometimes be confused with stroke. 15% have focal signs. Usually mild preceding febrile illness, headache and drowsiness. Sometimes fits, confusion and gradual-onset coma. Ophthalmoplegia, nystagmus, and other cranial nerve, cerebellar and sensory signs possible. Neck may not be stiff. CT scan may be normal. CSF usually abnormal.
Cerebral vasculitis	Difficult to diagnose. Primary or secondary (to temporal arteritis, amphetamines, cocaine, systemic lupus erythematosus, infection, etc.). Results in infarcts or bleeds. Headache prominent, focal neurological deficits, including cranial nerve palsies, or delirium. ESR can be raised, but this and other systemic markers will typically be normal in a primary central nervous system vasculitis. MRI and CSF abnormal. Check autoantibodies. May need angiography or temporal artery/brain/meningeal biopsy. Treat underlying cause and/or high-dose steroids.
Venous thrombosis	Difficult to diagnose. Most have headache, half have raised intracranial pressure (nausea, papiledema), some have focal neurological signs (hemiparesis or paraplegia) or fits. May be secondary to thrombophilia, trauma, infection or postpartum. CSF is often abnormal (raised pressure, high protein, few red and white cells). CT may show hyperdensity of cortical veins or sinuses (delta sign), filling defects with contrast (reversed delta sign), infarction, disproportionate swelling and hemorrhage. MR or CT venography is usually diagnostic.
Old stroke, with increased weakness	Old neurological signs are often worse during inter-current illness, especially infections, or appear to be so. Excluding a recurrent stroke is difficult, but rapid return to previous level of function is usual with appropriate treatment. Diffusion-weighted MRI may help.

with rt-PA, the goal is to complete CT examination within 25 minutes of arrival to the ER, with the study interpreted within an additional 20 minutes, and a subsequent CT often is obatined if the patient worsens neurologically and may be especially helpful in identifying hemorrhagic transformation following administration of rt-PA.

Parenchymal hemorrhage can be identified in deep brain structures in patients with hypertension or in atypical areas in patients without hypertension or under appropriate treatment, usually due to cerebral amyloid angiopathy. Infratentorial hemorrhage or cerebellar infarcts can be identified similar to supratentorial lesions, but smaller hemorrhages/ischemic infarcts, in particular in the brainstem, may easily be missed. In addition, CT may detect subarachnoid blood in the majority of cases with subarachnoid hemorrhage. Sometimes hemorrhages may even be interpreted as primary, but indeed are secondary to ischemic events. Involvement of clearly defined vascular territories is indicative of such conditions, which are easier to identify by magnetic resonance imaging (MRI) studies. Brain hemorrhages tend to grow in the first 6-12 h of stroke in about 40%-50% of all patients even without clinical deterioration, which makes a second early CT study necessary. If hemorrhages are not typically distributed, a venous infarction should be suspected[60]. In cases of venous thrombosis, delta sign and reverserd delta sign should be looked for. Delta sign represents a thrombosed venous sinus, not filled with contrast agent, representing reversed delta sign.

CT angiography (CTA) is a reliable tool to obtain information on extracranial and intracranial arterial patency, and its use in clinical practice often adds value to the diagnostic work-up[61].

Magnetic resonance imaging (MRI)

Standard MRI sequences (T1-weighted, T2-weighted, and proton density) are relatively insensitive to the changes of acute ischemia within the first hours after the onset of stroke, showing abnormalities in <50% of patients (Level I)[62], but are more sensitive than CT scanning for the display of intracerebral hemorrhage. Diffusion weighted MR is very sensitive for early detection of damaged brain tissue and in combination with perfusion weighted MR may help identify patients who benefit from early thrombolysis. In fact, current concepts suggest that patients with a significant perfusion-diffusion mismatch may benefit from restoration of the ischemic penumbra surrounding an already necrotic core of infarction, whereas those with overlapping areas of diffusion and perfusion deficits have a less favorable benefit/risk ratio. These MR techniques are not yet available on a large scale, but do seem promising tools for future routine applications. MR angiography (MRA) can be used to identify occlusions of major intracranial arteries but should carefully be interpreted if studies from extracranial cerebral arteries are missing. In this case, ultrasound can be useful to identify severe hemodynamically relevant carotid obstructions, which are likely to produce significant perfusion deficits in small embolic or lacunar strokes and may thus mimic falsely a remarkable perfusion-diffusion mismatch. MRA also has a role in evaluating the venous system and aneurysms down to a 3-mm diameter.

Neurosonography

Ultrasound studies are routinely performed in stroke centers. Their greatest advantage is the real-time, bedside evaluation of the morphology and hemodynamics of brain vessels. The major goal is to identify large obstructive lesions in the extracranial[63] as well as in the intracranial basal arteries[64-68]. In addition, transcranial Doppler (TCD) may be useful to monitor[65,69] and facilitate spontaneous or drug-induced thrombolysis in the majority of patients. It also enables differentiation of patients eligible for thrombolysis beyond three hours of stroke onset[70] and identifies the lesions amenable for interventional treatment[71]. The detection of rare causes of ischemic stroke such as dissections[72,73], intimal hyperplasia and other less frequent etiologies[74] is facilitated by the systematic use of ultrasound studies.

Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) was a randomized, double blind trial in symptomatic carotid stenosis, which demonstrated feasibility of TCD emboli detection to evaluate the efficacy of antiplatelet therapy[75], thus becoming a surrogate marker of stroke risk[73]. Preclinical manifestation of high cardiovascular risk can be ascertained with duplex measurement of the intima-media thickness (IMT) in the carotid artery on the neck, discriminating individuals at a low and high 1-year event stroke risk[76,77]. TCD provides real-time monitoring to detect hypoperfusion, embolism, thrombosis and recanalization in stroke patients and also during surgical and stenting procedures. It provides information on

vasospasm[78] as well as on the presence of aneurysms and other vascular malformations[79].

TCD offers information on the functional status of right-to-left shunts by means of emboli[80], lately becoming increasingly interesting in migraine patients with stroke and patent foramen ovale (PFO)[81], in transcatheter PFO closure[82] as well as in PFO closure in migraine[83].

Although nonimaging 300 kHz ultrasound tested in the TRanscranial low-frequency Ultrasound-Mediated thrombolysis in Brain Ischemia (TRUMBI) trial terminated prematurely due to the high rate of intracerebral hemorrhages, safe augmentation of TPA-asssociated thrombolysis with diagnostic 2 MHz TCD[84] can be further enhanced with addition of gaseous microbubbles[85]. This approach is now tested in a controlled multinational clinical trial of perflutren-containing microbubbles, which are not yet commercially available. A diagnostic 2 MHz TCCS 1-hour monitoring may be applied in stroke within 6 hours of stroke onset in patients ineligible for rt-PA[86].

Table 4. Requirements for center managing acute stroke patients

Minimum requirements for centres managing acute stroke patients	
1	Availability of 24-hour CT scanning
2	Established stroke treatment guidelines and operational procedures
3	Close co-operation of neurologists, internists and rehabilitation experts
4	Specially trained nursing personnel
5	Early multidisciplinary rehabilitation including speech therapy, occupational therapy and physical therapy
6	Established network of rehabilitation facilities to provide a continuous process of care
7	Neurosonological investigations within 24 h (extracranial color-coded duplex sonography of carotid and vertebral arteries and transcranial Doppler sonography of Willis circle and vertebrobasilar system)
8	ECG
9	Laboratory examinations (including coagulation parameters)
10	Monitoring of blood pressure, ECG, oxygen saturation, blood glucose, body temperature
Additional facilities recommended	
1	MRI/MRA
2	Diffusion and perfusion MR
3	MSCT angiography
4	ECG (transesophageal)
5	Cerebral angiography
6	Specialized neuroradiological, neurosurgical and vascular surgical c onsultation

Transesophageal and transthoracic echocardiography is frequently indicated in suspected cardioembolic stroke but is usually not performed on an emergency basis. It seems useful to have these studies available within the first 24 h of stroke onset to choose the best available secondary prevention, in particular in the presence of cardiac sources of embolism. They can also sometimes be identified by means of MCA monitoring if high intensity transient signals are observed.

Recent advances in the field of neurosonology[87] lead to Level 1 type A evidence that TCD and carotid duplex are recommended elements for a comprehensive stroke center[88].

Cardiac tests

Clinical cardiovascular examination and 12-lead electrocardiography (ECG) should be performed in all stroke patients. Cardiac abnormalities are prevalent among patients with stroke and the patient can have an acute cardiac condition that warrants urgent treatment. Acute myocardial infarction can lead to stroke, and acute stroke can lead to myocardial ischemia, or may occur at the same time. In addition, cardiac arrhythmias can occur in patients with acute ischemic stroke. Atrial fibrillation, an important potential cause of stroke, can be detected in acute setting. Cardiac monitoring can often be conducted after stroke to screen for serious cardiac arrhythmias.

Cerebrospinal fluid (CSF) analysis

Lumbar puncture and CSF analysis may sometimes be needed in dubious findings of CT scan or in vasculitis. It may differentiate between subarachnoid hemorrhage and infection, and may be useful in patients with subarachnoid hemorrhage and negative CT findings. It is necessary in centers without the option of CT scanning to calculate Allen score, which is 90% accurate in the identification of hemorrhage[89].

Laboratory tests

Several blood tests should be routinely perfomed (Table 5) to identify systemic conditions that may mimic (Table 3, Table 6) or cause stroke, or that may influence the choice of acute treatment. These include blood glu-

cose, electrolytes, complete blood count with platelet count, prothrombin time, activated partial thromboplastin time, renal and hepatic function studies. Because time is critical, therapy involving the use of rtPA in particular should not be delayed while waiting for the results of prothrombin time or activated partial thromboplastin time unless there is clinical suspicion of a bleeding abnormality or unless the patient has been taking warfarin and heparin or their use is uncertain.

Hypoglycemia may mimic the symptoms and signs of stroke, and hyperglycemia is associated with unfavorable outcome. A toxicology screen, blood alcohol level, and pregnancy test should be obtained if the physician is uncertain about the patient's history and/or suggested by findings on examination. Arterial blood gas levels should be obtained if hypoxia is suspected.

Table 5. Immediate diagnostic studies: evaluation of a patient with suspected acute stroke

All patients
Brain CT scan (brain MRI could be considered at qualified centers)
Electrocardiogram and chest X ray
Clinical chemistry
Complete blood count, including platelet count
Prothrombin time/international normalized ratio
Activated partial thromboplastin time
Serum electrolytes
Renal function tests
Hepatic function tests
Blood glucose
CRP, sedimentation rate
Pulse oximetry
Duplex and transcranial ultrasound
Selected patients
Toxicology screen
Blood alcohol determination
Pregnancy test
Oxygen saturation or arterial blood gas tests (if hypoxia is suspected)
Chest radiography (if lung disease is suspected)
Lumbar puncture (if subarachnoidal hemorrhage is suspected and CT is negative for blood, or suspected infection)
Electroencephalogram (if seizures are suspected)
MRI, MRA in selected cases, CTA
Diffusion MR and perfusion MR in selected cases in referral centers

Electroencephalography

Electroencephalography may be helpful for evaluating patients in whom seizures are suspected as the cause of neurological deficits or in whom seizure could have been a complication of stroke. Seizure is a relative contraindication for the use of rtPA in acute ischemic stroke.

Recommendations

1. Patients require a limited number of diagnostic tests as part of the emergency evaluation (Level I). Because time is crucial in acute stroke care, institutions should have these diagnostic studies available on a 24 hour/day and 7 day/week basis.
2. Cranial CT is the most important diagnostic tool in patients with suspected stroke (Level I). It distinguishes eligibility for specific stroke treatments and different stroke types, and rules out stroke mimics.
3. MRI/MRA can replace CT if perfomed appropriately, and in particular T2-weighted imaging is necessary to identify even small hemorrhages.
4. Early evalation of physiological parameters, blood chemistry and hematology, and of cardiac function is recommended in the management of acute stroke patients, and also to rule out metabolic causes of neurological symptoms. This also includes ECG, pulse, oximetry and chest x-ray.
5. Vascular imaging (neurosonology, CTA and MRA) in the acute condition gives additional information about the brain and neck vessel patency, and should supplement all imaging procedures already in the acute phase.
6. Neurosonological investigation of extra- and intracranial vessels (Level I) should be performed as part of comprehensive stroke treatment for noninvasive bedside evaluation of brain vessel morphology and hemodynamics.
7. Diffusion and perfusion MRI may be of additional help to assess the risk/benefit ratio of early revascularization therapy.
8. Cardiac ultrasound and specific hematology and serology tests for rare causes of stroke should be performed early after stroke, but should not delay general or specific treatment.

Table 6. Differential diagnosis of coma

Cause	Cause	Clues
Metabolic	Hypoglycemia	Glucometer
	Diabetic ketoacidosis or hyperosmolar coma	Glucometer, acidosis, ±ketonuria
	Hyper- or hyponatremia	Serum sodium
	Hypothermia/hyperthermia	Temperature
	Hepatic, uremic coma	Stigmata, flap, history, blood tests
	Septic encephalopathy	Fever, white count, inflammatory markers, focal signs or tests
	Myxedema coma/thyroid storm	History, clinical state, thyroid function tests
	Hypoxia/hypercapnia	History, pulse oxymetry, arterial blood gases
Trauma	Head injury	History, external signs, CT scan
Shock	Cardiogenic, pulmonary embolus, hypovolemic, septic, anaphylactic, drug-induced, addisonian, neurogenic	Pulse, BP, peripheral perfusion, urine output
Tropical infections	Malaria, typhoid, rabies, trypanosomiasis	Recent travel, temperature, blood tests
Neurological	Fits, status epilepticus, postconvulsive	History, convulsions, EEG
	Cerebral infarction/primary intracerebral hemorrhage/SAH	History, signs, CT scan
	Subdural or extradural hematoma	History of trauma. CT scan. Lucid interval after injury
	Meningitis, encephalitis	Fever, malaise, headache, neck and skin signs, CT scan, lumbar puncture
	Hypertensive encefalopathy	BP, fundus, urinalysis, renal function
	Brain tumor, abscess	CT scan
Psychogenic	Psychiatric or neurological examination	Eyes tight shut, pupils reactive, Doll's eye and caloric reflexes preserved, motor tone normal or inconsistent resistance to move ment, reflexes normal, EEG shown wakefulness

PART II
ACUTE STROKE MANAGEMENT

Therapy for acute stroke has three pillars. The first group can be addressed as general therapy. It deals with the management of all underlying serious medical conditions that need to be revised immediately. The second group is specific therapy that is directed against aspects of stroke pathogenesis. It effects either recanalization of the vessel occlusion or neuroprotection that is directed against several mechanisms of neural injury that occurs after brain ischemia. In hemorrhagic stroke, the mechanism of bleeding is to be determined and considered for acute surgical treatment or neuroradiological intervention. The third area of stroke treatment deals with complications occurring as sequels of acute stroke. These conditions can be divided into those of the neurologic origin (secondary hemorrhage, space occupying edema, seizures), and those not allied with neurologic condition of the patient (aspiration, infections, decubitus ulcers, deep vein thrombosis or pulmonary embolism). In parallel with the acute stroke patient treatment, the early secondary prevention aimed at reducing the incidence of early stroke recurrence is started, along with neurorehabilitation.

Monitoring of vital functions

To monitor vital functions and neurological condition accurately, frequent checks have to be made. Vital

functions or particular interest are: blood pressure, pulse rate, body temperature, blood gases, and blood glucose levels. The neurological status is best monitored using validated neurological scales such as the NIH Stroke Scale[90], the Scandinavian Stroke Scale[91] and the Glasgow Coma Scale[92].

In patients with a past medical history of cardiac disease and/or arrhythmias and in case of unstable blood pressure, on-line ECG monitoring is desirable. The electrodes for cardiac monitoring can also be used for respiratory monitoring, which is useful to detect respiration abnormalities during sleep[93]. When instrumental monitoring is not feasible, repeated ECG and clinical checks of respiratory function should be performed. Most of time, conventional blood pressure monitoring proves adequate; however, automatic inflatable units or mobile 24-h blood pressure devices should be available when necessary.

Respiratory status is verified and monitored through pulse oximetry or blood gases. A central venous catheter and occasionally central venous pressure monitoring is needed in severe stroke patients treated at specialized wards. *Via* a central venous catheter, indirect information on intravascular volume, cardiac function, and compliance within the venous system can be achieved.

GENERAL STROKE TREATMENT

It is not always neurological illness but the concurrent underlying medical conditions that are almost always present which are crucial for the prognosis of some patients. It has already been agreed that 'general treatment' refers to treatment strategies aimed at stabilizing the critically ill patient, in order to control systemic problems that may adversely influence stroke outcome and to provide an optimum physiological basis upon which specific therapeutic strategies may be applied. There is a consensus that the management of general medical problems is the basis of stroke treatment[21,94-97]. General management of stroke patients includes respiratory and cardiac care, fluid and metabolic management, blood pressure control, and treatment of elevated ICP if needed. Also, there is treatment of seizures and prophylactic measures concerning deep vein thrombosis, pulmonary embolism, dysphagia, aspiration pneumonia, other infections and decubital ulcers as part of the general treatment of stroke patients.

General stroke treatment is equally applied in specialized units as at general hospital wards. Although the proposed management of hypertension, hyperglycemia or fever has never been separately tested prospectively, the stroke outcome has ameliorated. Despite this, the prognosis for patients treated in stroke units is better when early therapeutic actions are taken immediately.

Pulmonary function and airway protection

Maintaining adequate tissue oxygenation is of great importance during periods of acute cerebral ischemia in order to prevent hypoxia and preserve metabolic function in the ischemic penumbra, and thus to prevent the potential worsening of the neurological injury. Still, there are no data from prospective clinical trials to corroborate this assumption. The most common causes of hypoxia are partial airway obstruction, hypoventilation, aspiration pneumonia, heart failure, pulmonary embolism or exacerbation of chronic obstructive pulmonary disease, or atelectasis. Patients with a decreased level of consciousness or brainstem stroke have an increased risk of airway compromise due to impaired oropharyngeal mobility and loss of protective reflexes. In patients with sustained seizure activity, a plugged airway may be present. Following stroke, some patients develop Cheyne-Stokes respiration with a decrease in oxygen saturation that can be readily reversed with oxygen supplementation. Ventilation may be particularly compromised during sleep.

Respiratory function has to be monitored in order to detect and treat hypoxia. Pulsed oximetry is applied with a target oxygen saturation level of $^{3}95\%$. Supplemental oxygen should be administered if there is evidence of hypoxia by blood gas determination, desaturation detected by pulse oximetry, or there are other specific reasons. Blood oxygenation is improved by the administration of 2-4 liter of O_2 *per* minute *via* a nasal tube. Early endotracheal intubation is recommended in the event of a pathologic respiratory pattern, severe hypoxemia or hypercarbia, and in unconscious patients (Glasgow Coma Scale <8) at a high risk of aspiration. Prognosis of stroke patients undergoing intubation is thus better than usually thought, with a one-year survival rate of almost one-third if not invariably poor[98,99]. Before intubation is performed, the general prognosis, coexisting life-threatening medical conditions and the patient family consent must be considered and obtained.

There are insufficient data on the utility of hyperbaric oxygen to recommend this therapy for most patients with stroke.

Cardiac care and hemodynamic stability

Myocardial infarction (MI) and cardiac arrhythmias are potential complications of acute ischemic stroke. Patients with infarctions in the right hemisphere may have a high risk of arrhythmias, presumably due to disturbances in sympathetic and parasympathetic nervous system function. Irrespective of previous cardiac disease, a correlation was found between infarcts involving the insular cortex and cardiac complications[100]. Electrocardiographic changes secondary to stroke, mimicking myocardial ischemia, may appear[101], and include ST segment depression, QT interval prolongation, inverted T waves, and prominent U waves. Cardiac enzymes may be elevated after stroke[102]. Most of the events are related to pre-existing coronary artery disease[103], but acute or subacute myocardial infarction is a potential complication related to the release of catecholamines. The most common arrhythmia secondary to stroke is atrial fibrillation (AF)[104,105]. While life-threatening cardiac arrhythmias are relatively uncommon, heart failure, acute MI or sudden death[104,106] may complicate the clinical course.

Every stroke patient should have an initial ECG, while indications on continuous ECG monitoring are reported above.

Optimizing cardiac output with maintenance of a high normal blood pressure 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 routinely used, will give early warning of hemodynamic instability. Both volume deficiency and overload have adverse effects on cerebral perfusion. Therefore, 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 blood pressure. Dopamine may be particularly useful in patients with arterial hypotension or renal insufficiency. Increases in cardiac output may increase cerebral perfusion in the areas which have lost their autoregulatory capacity after acute ischemia. Restoration of normal cardiac rhythm using drugs, cardioversion, or pacemaker support should be performed in cooperation with internists and cardiologists.

Blood pressure management

Blood pressure monitoring and treatment is a critical issue, since many patients with acute stroke have elevated blood pressure[107], and its optimal management has not been estalished. Some data favor treatment[107-111], but evidence opposing treatment is also available[107,111,112]. Cerebral blood flow autoregulation may be defective in an area of evolving infarction[115]. The elevated blood pressure can result from the stress of stroke, a full bladder, pain, pre-existing hypertension, a physiological response to hypoxia, or increased ICP. Theoretical reasons to lower blood pressure include reducing the formation of brain edema, lessening the risk of hemorrhagic transformation of the infarction, preventing further vascular damage, and forestalling early recurrent stroke. However, aggressive treatment of elevated blood pressure reduced the flow in the ischemic penumbra that is passively dependent on the mean arterial pressure[116], and may expand the size of the infarction. Hence, abrupt drops in blood pressure must be avoided if an adequate cerebral perfusion pressure is to be maintained.

Because of these conflicting issues and the lack of unambiguous data, the appropriate treatment of blood pressure in the setting of acute ischemic stroke remains controversial. In the majority of patients, a decline in blood pressure will occur without any specific medical treatment[117-120]. The blood pressure often falls spontaneously when the patient is moved to a quiet room, the bladder is emptied, pain is controlled, and the patient is allowed to rest. In addition, treatment of elevated ICP can result in a decline in arterial blood pressure.

Although there are no definitive data from controlled clinical trials, in the absence of other organ dysfunction necessitating rapid reduction in blood pressure, or in the setting of thrombolytic therapy, there is little scientific basis and no clinically proven benefit for lowering blood pressure in patients with acute ischemic stroke[121]. In most circumstances, blood pressure should generally not be lowered. Situations that might require urgent antihypertensive therapy include hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, or acute MI (although extreme lowering of blood pressure is deleterious for MI patients as well)[122].

A target systolic blood pressure of 180 mm Hg and diastolic blood pressure of 100-105 mm Hg is recommended in patients with prior hypertension. In other cases, lower blood pressure values are desirable (160-180/90-100 mm Hg). Obviously, extremely high blood pressure levels are not acceptable. Systolic values over 220 mm Hg or diastolic values over 120 mm Hg constitute an indication for early but cautious drug treatment,

avoiding a drastic or abrupt reduction in blood pressure (Table 7). In patients undergoing thrombolysis or heparin administration, systolic blood pressure above 180 mm Hg should be avoided.

Besides ischemic stroke, the antihypertensive treatment is also indicated in a non-ischemic cause of stroke, such as subarachnoid hemorrhage, intracerebral hemorrhage or subdural hematoma.

When treatment is indicated, lowering of blood pressure should be done cautiously. Parenteral agents such as labetalol (10 mg) that are easily titrated and that have minimal vasodilatory effects on cerebral blood vessels are preferred and recommended by the European Stroke Initiative[21] and American Stroke Association[23] but at this time are not available in Croatia. In some cases, an intravenous infusion of sodium nitroprusside may be

Table 7. Approach to elevated blood pressure in acute ischemic stroke

Blood pressure level (mm Hg)	Treatment
Systolic <220 or diastolic <120	Observe unless other end-organ involvement, e.g. aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy Treat other symptoms of stroke such as headache, pain, agitation, nausea and vomiting Treat other acute complications of stroke, including hypoxia, increased intracranial pressure, seizures or hypoglycemia
Systolic ≥220 and/or diastolic 120-140, on repeat measurements	Captopril 6.25-12.5mg (p.o./i.m.) Labetalol 5-20mg iv.* ** Urapidil 25mg iv./15 min.***, followed by 120 mg/h iv, parallel with usual antihypertensive treatment, and maintenance 8.8 mg/h iv. Clonidine 0.15-0.3 mg iv. or sc. Dihydralazine 5mg iv. plus metoprolol 10mg
Diastolic ≥140	Nitroglycerin 5mg iv, followed by 1-4mg/h Sodium nitroprusside 1-2mg
Eligible for thrombolytic therapy ***Pretreatment*** Systolic >185 or diastolic >110	Labetalol 10-20mg iv over 1-2 min*, may repeat once or nitropaste Urapidil 25mg iv./15 min., followed by 120 mg/h iv, parallel with usual antihypertensive treatment If blood pressure is not reduced and maintained at desired levels (systolic ≤180 and diastolic ≤110), do not administer rt-PA
During and after treatment 1. monitor BP 2. diastolic >140 3. systolic >230 or diastolic 121-140 4. systolic 180-230 or diastolic 105-120	1. Check BP every 15 minutes for 2 hours, then every 30 minutes for 6 hours, and then every hour for 16 hours 2. Sodium nitroprusside 0.5 mg/kg/min iv infusion as initial dose and titrate to desired blood pressure 3. Labetalol 10mg iv over 1-2 min*, may repeat or double labetalol every 10 min to max dose of 300mg or give initial labetalol bolus and then start labetalol drip at 2-8 mg/min Or Nicardipine 5mg/h iv infusion as initial dose, titrate to desired effect by increasing 2.5 mg/h every 5 min to max of 15mg/h. If BP is not controlled by labetalol, consider sodium nitroprusside 4. Urapidil 25mg iv./15 min., followed by 120 mg/h iv, parallel with usual antihypertensive treatment, and maintenance 8.8 mg/h iv.

* If available (at this time in Croatia not available)

** Avoid labetalol in patients with asthma, cardiac failure, severe conduction abnormalities and bradycardia

*** May cause abrupt hypotension

necessary for appropriate blood pressure control. Patients can also be treated with oral agents such as captopril (6.25-12.5 mg), having short duration of action and an abrupt effect, or nicardipine. Sublingual use of a calcium antagonist such as nifedipine should be avoided because of rapid absorption and a secondary precipitous decline in blood pressure[123], possible ischemic steal[21,112,114,121], and overshoot hypertension. Intravenous urapidil is increasingly used in this situation (Table 7). Finally, sodium nitroprusside is sometimes recommended despite the possible major side effects such as reflex tachycardia and coronary artery ischemia.

Among patients who are candidates for treatment with thrombolytic agents, careful management of blood pressure is critical before and during the administration of rtPA and during the ensuing 24 hours[113] because excessively high blood pressure is associated with parenchymal hemorrhage[124]. Thrombolytic therapy is not given to patients who have a systolic blood pressure >185 mm Hg or a diastolic blood pressure >110 mm Hg at the time of treatment.

A low or normal-low blood pressure at stroke onset is unusual[107], but if present, the cause should be sought. The causes include aortic dissection, volume depletion, decreased cardiac output secondary to myocardial ischemia or cardiac arrhytmias. Correction of hypovolemia and optimization of cardiac output are important priorities during the first hours after stroke. Treatment includes volume replacement and correction of arrhythmias, such as slowing ventricular response to rapid AF. Blood pressure can be raised by adequate patient rehydration with crystalloid (saline) or, occasionally, colloid solutions, and underlying disease management. Low cardiac output may need inotropic support.

Glucose metabolism

Diabetes mellitus (DM) is an important risk factor for ischemic vascular disease. The severity of strokes may be increased among diabetic patients. An increase in serum glucose levels on hospital admission may be found in both diabetic[125,126] and non-diabetic patients. Several clinical studies have associated hyperglycemia with poor outcomes[127-130]. This is true not only for diabetic patients, whose metabolic derangement may be dramatically worsened in the acute stroke phase, but also for non-diabetic subjects[129,130]. Therefore, temporary insulin treatment may become necessary. A blood glucose of 10 mmol/L or higher justifies immediate insulin titration. Unless the blood glucose level is known, no glucose solution should be given to a stroke patient.

Because hypoglycemia can cause focal neurological signs that mimic stroke[131] and because severe hypoglycemia can itself lead to brain injury, prompt measurement of the serum glucose concentration and rapid correction of a low serum glucose concentration should be treated by intravenous dextrose bolus or infusion of 10%-20% glucose, preferably *via* a central venous line.

Body temperature

Elevated body temperature in the setting of acute stroke has been associated with poor neurological outcome[132-134] (Level I), possibly due to increased metabolic demands, enhanced release of neurotransmitters, and increased free radical production, thus increasing infarct size[135]. It has to be remembered that infection is a risk factor for stroke[136,137]. The source of fever following stroke should be ascertained in order to start tailored treatment. Treating elevated temperature in stroke patients is advisable because it might improve the prognosis of patients with severe events[138]. Measures can include antipyretic medications[134] and cooling devices.

Hypothermia has been shown to be neuroprotective after experimental global and focal hypoxic brain injury[139]. Small clinical studies have addressed the feasibility of inducing modest hypothermia for treatment of patients with acute ischemic stroke; however, the efficacy of this approach has to be evaluated in larger trials.

Fluid and electrolyte management

In hemorrhagic stroke or SAH, serious electrolyte abnormalities are frequent. Contrary to this, in ischemic stroke they can rarely be found[140]. A balanced fluid and electrolyte status should be kept to avoid plasma volume contraction, raised hematocrit, and impairment in the blood rheologic properties, which may influence brain perfusion and kidney function. Some degree of dehydration on admission is frequent and may be related to poor outcome[141]. Virtually all acute stroke patients need intravenous fluid therapy, with a more or less positive balance according to the level of dehydration. However, uncontrolled volume replacement may lead to cardiac failure and pulmonary edema. A slightly negative fluid balance is recommended in the presence of brain edema. Hypotonic solutions (NaCl 0.45% or glucose 5%) are contraindicated due to the risk of brain edema increase.

Electrolytes should be monitored daily and substituted accordingly. A peripheral venous access is needed for initial fluid management and blood sampling, while a central venous catheter is required in case of infusion of larger volumes of fluids or hyperosmolal solutions.

Recommendations

1. Neurological status and vital functions should be monitored.
2. Oxygenation monitoring with pulse oximetry is recommended (Level III).
3. O_2 administration is recommended in case of hypoxemia (blood gas analysis or O_2sat <92% at pulse oximetry) (Level III).
4. Airway support and ventilator assistance may be recommended in patients with depressed levels of consciousness or airway compromise (Level III).
5. Nonhypoxic patients with acute ischemic stroke do not need supplemental oxygen therapy (Level II).
6. There are insufficient data on the utility of hyperbaric oxygen to recommend this therapy for most patients with stroke.
7. Intubation is recommended in case of potentially reversible respiratory insufficiency.
8. Continuous cardiac monitoring is recommended in the first 48 h of stroke onset, especially in patients with: (a) previous known cardiac disease, (b) history of arrhythmias, (c) unstable blood pressure, (d) clinical signs/symptoms of heart failure, (e) abnormal baseline ECG, and (f) infarct involving the insular cortex (Level III).
9. Routine blood pressure lowering is not recommended, except for extremely elevated values (SBP >200-220 mm Hg or DBP >120 mm Hg for ischemic stroke and >180/105 for hemorrhagic stroke) confirmed by repeated measurements (Level III).
10. Immediate antihypertensive therapy for more moderate hypertension is recommended in case of stroke and hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, acute myocardial infarction or heart failure, thrombolysis or intravenous heparin, but should be applied cautiously (Level III).
11. Recommended target blood pressure in patients (a) with prior hypertension: 180/100-105 mm Hg; (b) without prior hypertension: 160-180/90-100 mm Hg; and (c) under thrombolysis avoid systolic blood pressure above 180 mm Hg (Level III).
12. Recommended drugs for blood pressure treatment are: (a) intravenous labetalol, if available, or urapidil; and (b) intravenous sodium nitroprusside, nitroglycerin or oral captopril (Level III).
13. Nifedipine and any drastic blood pressure decrease should be avoided (Level III).
14. Hypotension should be avoided, and treated, particularly in unstable patients. The source should be seeked and treated, and adequate amounts of fluids should be adminstered and, when required, volume expanders and/or catecholamines (epinephrine 0.1-2 mg/h plus dobutamine 5-50 mg/h) (Level III).
15. Monitoring of serum glucose levels is recommended, particularly in known diabetic patients (Level III).
16. Glucose solutions are not recommended due to the detrimental effects of hyperglycemia (Level III).
17. Treatment of serum glucose levels >10 mmol/L with insulin titration is recommended (Level III). Management of an elevated blood glucose level following stroke should be similar to that given to treatment of other acute ill patients who have hyperglycemia. Blood glucose concentrations should be monitored. Overly aggressive therapy should be avoided because it can result in fluid shifts, electrolyte abnormalities and hypoglycemia, all of which can be detrimental to the brain.
18. Immediate correction of hypoglycaemia is recommended by intravenous dextrose bolus or infusion of 10%-20% glucose (Level III).
19. Treatment of body temperature >37.5 °C is recommended with antipyretic medication and cooling devices (Level III).
20. In case of fever, the search for possible infection (site and etiology) is recommended, in order to start tailored antibiotic treatment (Level III).
21. Prophylactic administration of antibiotic, antimycotic or antiviral medication in immunocompetent patients is not recommended (Level III).
22. There are insufficient data about the usefulness of induced hypothermia to recommend this treatment.
23. Monitoring and correction of electrolyte and fluid disturbances are recommended (Level III).
24. Hypotonic solutions (NaCl 0.45% or glucose 5%) are contraindicated due to the risk of brain edema increase consequent to the reduction of plasma osmolality (Level III).

SPECIFIC ISCHEMIC STROKE TREATMENT

Because most strokes are caused by thromboembolic occlusion of an intracranial artery, restoration or improvement of perfusion to the ischemic area is a key therapeutic strategy. The concept of the existence of an ischemic penumbra is fundamental to the current approach to ischemic stroke treatment: although the core of infarcted tissue might not be salvageable, adjacent dysfunctional tissue might be saved if the circulation is restored and the metabolism is normalized. A number of strategies have been employed to improve blood flow to the ischemic region. Because of the dynamic consequences of acute stroke, the interval from the onset of symptoms to treatment appears to be critical for success of any therapy. Thus, restoration of blood flow needs to be achieved as quickly as possible.

Thrombolytic therapy

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA), 0.9 mg/kg body weight, given within 3 hours after stroke onset in patients with acute ischemic stroke significantly improves the outcome of stroke[142-148], with an NNT of 7. Two European trials, ECASS and ECASS II, tested the 6-hour time window and did not show statistically significant superiority of rt-PA for the primary endpoints[142,144].

There have thus far been 18 completed, randomized, controlled trials of thrombolytic therapy *versus* control in 5,727 highly selected patients[149,150]. The thrombolytic agents tested were urokinase (UK), streptokinase (SK), recombinant tissue plasminogen activator (rt-PA), and recombinant pro-UK. About 50% of data (patients and trials) come from trials testing intravenous rt-PA. Treatment allocation was double-blind in 16 of 18 trials. Thrombolysis was administered by the i.v. route in 16 trials (98% of patients), and by intra-arterial route in two trials. As different thrombolytic drugs were compared in only three trials, and with a very small number of patients (n=688) and outcome events, and no statisticaly significant difference was shown among different agents[151], they were considered together in pool analysis in order to maximize statistical power. Thrombolysis within 6 h of the onset of ischemic stroke was associated with a significant, 5-fold increase in fatal intracranial hemorrhage (5.2% of thromolysis, 0.9% of control), and a 3-fold increase in early symptomatic intracranial hemorrhage (8.7% of thrombolysis, 2.5% of control), with no significant heterogeneity between thrombolytic agents or trials[149,150]. Despite an excess early hazard, thrombolysis administered up to 6 hours after ischemic stroke was associated with a significant reduction in death or dependency (m RS 3-6) at the end of follow-up 3-6 months after randomization (53.3% of thrombolysis, 58.0% of control; OR 0.84, 95% CI: 0.75-95; 2P=0.004)[149]. This represents 43 (95%CI: 13-71) fewer dead or dependent patients *per* 1000 treated with thrombolysis compared with control. There was no significant heterogeneity of treatment effect among the trials (p=0.09), indicating that the favorable treatment effect was qualitatively the same in all trials. This is reflected in the subgroup of trials using i.v. rt-PA, where there was a similar reduction in death or dependency. However, there was significant heterogeneity of the treatment effect among trials using rt-PA (p=0.02).

Eight phase III trials tested rt-PA in 2,889 patients. Overall, there was a significant reduction in the number of patients with poor functional outcome (combined death or dependency) at the end of follow-up (OR 0.83, 95% CI 0.73-0.94). The subgroup analysis showed that patients treated within 3 h had a greater reduction in poor functional outcome with thrombolysis (OR 0.58, 95% CI 0.46-0.74), with no adverse effect on death[152-154].

A pooled analysis of individual data of the six rt-PA trials confirms that thrombolysis works at least until 4.5 h and potentially up to 6 h after stroke onset[148]. Caution is advised before giving intravenous rtPA to persons with severe stroke (NIH Stroke Scale >25), or if CT demonstrates extended early changes of a major infarction, such as sulcal effacement, mass effect and edema.

Thrombolytic therapy 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 reading this imaging study. Because the use of thrombolytic drugs carries the real risk of major bleeding, the risks and potential benefits of rt-PA should be discussed whenever possible with the patient and family before treatment is initiated. Table 8 contains contraindications for rt-PA thrombolytic treatment. Table 9 contains guidelines for the management of intracranial hemorrhage after thrombolysis.

Intravenous administration of rt-PA more than 3 h after stroke should only be given in an institutional protocol as experimental therapy or within a multicenter clinical trial, and is at present being tested in the ECASS

3 and IST 3 trials, which randomize patients on clinical and CT grounds, within up to 4.5 and 6 hours of the event, respectively. The Desmoteplase in Acute Ischemic Stroke (DIAS) and the Dose Excalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trials randomized ischemic stroke patients to different doses of desmoteplase, according to the MRI evidence of a PW/DW mismatch in the time window between 3 and 9 hours after stroke onset[155]. Continuous auditing of routine use of thrombolytic therapy is advisable.

The Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST) is the post-marketing surveillance study required by the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) in Europe, as a condition for the approval of thrombolysis with rt-PA within 3 h of onset of acute ischemic stroke. It began in January 2003, and every 6 months data are reported to the EMEA and a statement is published at the study web site (www.acutestroke.org). On the last report released in December 2005, more than 4,000 patients in more than 250 centers had been treated. Symptomatic intracerebral hemorrhage and motality rates were lower than in the randomized clinical trials, while the percentage of patients reaching an mRS score of 0 to 2 at 3-month follow-up was comparable to that in randomized clinical trials, without remarkable differences between more and less expert centers.

Table 8. Contraindications for rt-PA thrombolytic treatment

1. Ischemic stroke >3 hours from stroke onset
2. Brain CT signs of intracranial hemorrhage
3. Brain CT or MR signs of acute stroke
4. Small (NIHSS<4) or large (NIHSS>22) neurological deficit or quick symptom regression
5. Clinical evidence of SAH, but brain CT negative
6. History of intracranial bleeding, arteriovenous malformations, aneurysm or brain tumor
7. Stroke or head trauma within 3 months
8. Systolic BP <185 mm Hg or diastolic BP >110 mm Hg on repeat measurements
9. Arterial catheterization at the site that is not compressible or lumbar puncture within a week
10. Operation or major injury within two weeks
11. Gastrointestinal bleeding or urinary tract bleeding within three weeks
12. Platelets <100 000 mm^3
13. APT exceeding control values due to heparin treatment within 48 hours
14. Oral anticoagulation treatment, PT <15 or INR <1.7
15. Seizure as initial stroke presentation
16. Glucose levels <2.78 or >22.2 mmol/L
17. Recent myocardial infarction, bacterial endocarditis or pericarditis
18. Pregnancy

Table 9. Management of intracranial hemorrhage after thrombolysis

Suspect intracranial hemorrhage if:
1. Acute neurological deterioration (>2 points NIHSS scale)
2. New headache
3. Nausea or vomiting
4. Acute increase in BP

If intracranial hemorrhage is suspected:
1. Discontinue rt-PA
2. Organize urgent brain CT scan
3. Blood: FBC, APTT, INR, fibrinogen, cross match
4. Call hematologist to provisionally request cryoprecipitate and platelets

If hemorrhage:
1. Administer cryoprecipitate 1 unit/10 kg body weight and platelets 6-12 units
2. If rt-PA is still circulating at the time of the bleeding onset and immediate control of bleeding is required: consider antifibrinolytic therapy (e.g. i.v. aminocaproic acid 0.1 g/kg over 30 min or aprotinin 2 million kallikreain inhibitory units over 30 min), while awaiting cryoprecipitate
3. Consult neurosuregon if decompressive surgery indicated
4. Recheck FBC, APTT, INR, fibrinogen after administration of cryoprecipitate and platelets, and target further administration of cryoprecipitate if fibrinogen levels remain <1.0 g/L, in consulatation with hematologist.

In case of bleeding elsewhere, cease rt-PA and investigate and treat as clinically indicated. The principles regarding use or cryoprecipitate, platelets and antifibrinolytic therapy are the same. In addition: call blood bank to arrange cross-match in case transfusion of fresh frozen plasma is required.

Consult gastroenterologist or urologist as clinically indicated.

The SITS-MOST study closed on April 30 (last patient in) and definite results are awaited by the end of this year.

Intravenous streptokinase has been shown to be associated with an unacceptable risk of hemorrhage and hemorrhage-associated death[156,157] (Level I). The dose of streptokinase was 1.5 million units, the same given to MI patients, and may have been too high for treatment of stroke patients. In addition, treatment was initiated up to 6 hours after the onset of symptoms. The trials also enrolled seriously ill patients, who were at a high risk of bleeding complications. However, there remains no evidence that intravenous streptokinase is of benefit in patients with acute ischemic stroke.

Other intravenously administered thrombolytic agents including reteplase, urokinase, anistreplase and staphylokinase might be considered for treatment of patients with acute ischemic stroke. None of these agents has been tested extensively.

Ultrasound enhanced thrombolysis

Ultrasound is believed to have a thrombolytic capacity that can be used for pure mechanical thrombolysis (with high intensities (>2 W/cm2) or improvement of enzyme-mediated thrombolysis (with lower intensities)[158]. The trial was prematurely stopped because of the high rate (36%) of symptomatic intracranial hemorrhages and no signal of efficacy on early recanalization or clinical outcomes at 3 months.

A small phase II randomized controlled clinical trial suggests that continuous 2 MHz, single-element pulsed-wave TCD ultrasonography that is aimed at residual obstructive intracranial blood flow, may help expose thrombi to rt-PA and enhance the thrombolytic activity of t-PA. Among 126 patients randomly assigned to receive continuous ultrasonography (63 patients) or placebo (63 patients), complete recanalization or dramatic clinical recovery within 2 h of the administration of a t-PA bolus occurred in 31 patients in the treatment group (49%), as compared with 19 patients in the control group (30%; p=0.03)[84]. There was no increase in symptomatic intracranial hemorrhages (three patients in the target and control group each). At 3 months, a favorable outcome (mRS of 0 or 1) was achieved in 22 of 53 (42%) patients in the treatment group who were eligible for follow-up and 14 of 49 (29%) patients in the control group (p=0.20). The ultrasound mediated thrombolysis can be further enhanced with the addition of gaseous microbubbles[85]. This approach is now being tested in a controlled multinational clinical trial of perflutren-containing microbubbles, which are not yet commercially available. A diagnostic 2 MHz TCCS 1-hour monitoring may be applied in stroke within 6 hours of stroke onset in patients not eligible for rt-PA[86].

Defibrinogenating enzymes

Ancrod is a defibrinogenating enzyme which was shown to improve outcome after acute ischemic stroke if given within 3 h after stroke onset and over 5 days[159]. Recently, a European trial testing ancrod treatment in a 6-hour time window had to be terminated prematurely and did not confirm the US findings.

Intra-arterial thrombolysis

Intra-arterial thrombolytic therapy of occlusions of the proximal part of the MCA using prourokinase has been shown to be significantly associated with better outcome in a randomized trial (MCA recanalization was achieved in 66% of r-proUK treated patients and in 18% of controls). This treatment is safe and efficacious in a 6-hour time window, but it requires super-selective angiography and is only available in selected centers[160]. Intra-arterial treatment of acute basilar occlusion with urokinase or rtPA is frequently used in selected centers, but has not been subjected to a randomized trial[161].

Recommendations

1. Intravenous rt-PA (0.9 mg/kg, maximum 90 mg), with 10% of the dose given as a bolus, followed by an infusion over 60 min, is the recommended treatment within 3 h of the onset of ischemic stroke (Level I). The safety and efficacy of rtPA for treatment of pediatric patients have not been established. Patients with major strokes (NIHSS >22) have a very poor prognosis whether or not they are treated with rtPA, and the risk of hemorrhage is high. They may still benefit from the treatment.
2. The benefit from the use of intravenous rtPA for acute ischemic stroke beyond 3 h after the onset of symptoms is smaller, but is present for up to 4.5 h (Level I).
3. Intravenous rt-PA is not recommended when the time of stroke onset cannot be ascertained reliably; this includes persons whose strokes are recognized upon awakening (Level IV).

4. Intravenous administration of streptokinase is dangerous and not indicated for the management of persons with ischemic stroke (Level I).
5. Data on the efficacy and safety of any other intravenously administered thrombolytic drugs are not available to provide a recommendation.
6. A diagnostic, continuous 2 MHz, TCD ultrasonography, aimed at residual obstructive intracranial blood flow, in combination with previously recommended rt-PA treatment within 3 h of onset of ischemic stroke, may improve the outcome (Level III).
7. A diagnostic, continuous 2 MHz TCD or TCCS 1-hour monitoring may be applied in stroke within 6 hours of stroke onset in patients ineligible for rt-PA (Level IV).
8. Intra-arterial treatment of acute MCA occlusion in a 6-hour time window using prourokinase results in a significantly improved outcome (Level II).
9. Acute basilar occlusion may be treated with intra-arterial therapy at selected centers in an institutional protocol as experimental therapy or within a multicenter clinical trial (Level IV).
10. At present, ancrod cannot be recommended for use in acute ischemic stroke outside the setting of clinical trials.

Platelet inhibitors

Two large randomized, non-blinded interventional studies have shown that aspirin given within 48 h after stroke[162,163] reduces mortality rate and rate of recurrent stroke minimally but statistically significantly[162,163], with an NNT of 111. A meta-analysis from these trials including 40,000 stroke patients[164] has shown that the prompt use of aspirin should be routinely considered for all patients with suspected acute ischemic stroke, even when CT scan is not available, mainly to reduce the risk of early recurrence.

Aspirin should not be used if rt-PA thrombolysis is planned or for 24 hours after its administration.

Early anticoagulation

Although early anticoagulation with unfractionated heparin (UFH) has been frequently used in the treatment of acute ischemic stroke, it has not proved overall benefit due to the higher rate of hemorrhagic complications. None of the early anticoagulation trials performed over the past years has proved the influence of heparin on stroke outcome or recurrent stroke reduction[165]. While there was some kind of improvement in outcome or reduction in stroke recurrence rates[166], this was almost always counterbalanced by an increased number of hemorrhagic complications.

Also, low-molecular-weight heparins and heparinoids (LMWHs) were analyzed in a systematic meta-analysis[167]. LMWHs reduce venous thromboembolic events in patients with acute ischemic stoke and increase the risk of extracranial bleeding. A nonsignificant reduction in combined death and disability, and nonsignificant increases in case fatality and symptomatic intracranial hemorrhage were also observed. There is a general agreement that heparins should not be used in the routine management of patients with ischemic stroke. Recently, a promising article has appeared on the use of UFH in acute stroke patients[168]. Some 418 selected patients were randomly treated within 3 hours after stroke onset with intravenous heparin sodium (activated partial thromboplastin time ratio 2.0-2.5) or saline for 5 days. Safety end points were death, symptomatic intracranial hemorrhage (sICH), and major extracranial bleedings by 90 days of stroke; the efficacy end point was a mRS 0-2 at 90 days. In the heparin group the rate of sICH was significantly increased (6.2% *vs.* 1.4%; p=0.008). Despite this increased bleeding risk, at 90 days a significantly higher proportion of self-independent patients were found among heparin treated patients (38.9% *vs.* 28.6%, p=0.025). This positive effect is of particular interest because the mean NIHSSS at randomization was 17 in both treatment groups. These findings will call for reconsidering therapeutic strategies in most international stroke societies for further acute stroke management for patients in whom thrombolytic therapy is contraindicated within a 3-hour time window.

Up to now, most investigators agree that full-dose heparin may be used in selected indications such as cardiac sources with high risk of re-embolism, arterial dissection or high-grade arterial stenosis prior to surgery (Table 10), although present data indicate that the early administration of the tested, rapidly acting anticoagulants does not lower the risk of early recurrent stroke, including patients with cardioembolic stroke (Level I). Early administration of anticoagulants does not lessen the risk of neurological worsening (Level I). There are no adequate data to demonstrate the efficacy of anticoagulants in potentially high-risk groups such as those patients with intracardiac or intra-arterial thrombi. The efficacy of urgent anticoagulation is not established for treatment of patients with vertebrobasilar artery disease

or arterial dissection. A subgroup analysis from one trial of urgent administration of danaparoid[169] found that an anticoagulant might improve the chances of favorable outcomes among patients with stroke secondary to large artery atherosclerosis (Level II).

Dissections of carotid and vertebral arteries

Dissections of the carotid and vertebral arteries are now recognized as relatively common causes of stroke, particularly among young patients. Dissections lead to ischemic strokes through artery-to-artery embolism or by causing significant stenosis and occlusion of the proximal vessel, and in some cases, dissections may lead to formation of a pseudoaneurysm, which can also serve as a source of thrombus formation. Intracranial dissections in the vertebrobasilar territory have a higher risk of rupture, leading to SAH. The goals of therapy when treating patients with dissections and ischemic stroke are to prevent further ischemic strokes and to promote healing of the dissected vessel. Studies have shown that the risk of recurrent stroke and dissection is low, typically in the range of 1%-4% over the next 2-5 years[170], although many of the patients were treated with anticoagulants or antiplatelet agents for several months, and it is difficult to determine the natural history rate of recurrence. Although it is often stated that treatment with intravenous heparin, followed by 3-6 months of therapy with oral anticoagulants, is routine care for patients with a carotid or vertebral dissection (with or without an ischemic stroke), there are no data from prospective randomized studies supporting such an approach. Some data suggest that intravenous heparin may be effective for preventing further artrial embolization in the setting of cervical dissections[171-173]. Heparin and similar agents may also promote or hasten the dissolution of the intramural thrombus found in many patients with dissections, thereby promoting healing of the dissection[173,174]. The risk of heparin causing hemorrhagic transformation in these patients appears to be low (<5%). The use of heparin or other anticoagulants in patients with SAH related to a dissection is contraindicated.

Table 10. Remaining indications for heparin treatment after stroke

Stroke due to cardiac emboli with high risk of re-embolization (artificial valves, atrial fibrillation, myocardial infarction with mural thrombi, left atrial thrombosis)
Coagulopathies such as protein C and S deficiency, APC resistance
Symptomatic dissection of extracranial arteries
Symptomatic extra- and intracranial stenoses
Symptomatic internal carotid stenosis prior to operation
Crescendo TIAs or stroke in progression
Sinus venous thrombosis

Cerebral venous sinus thrombosis

Two small randomized trials of anticoagulant therapy were performed in patients with cerebral venous sinus thrombosis[175,176]. The first trial compared dose-adjusted UHF (partial thromboplastin time at least twofold the control one) with placebo. The study was terminated early, after only 20 patients enrolled, because of the superiority of heparin therapy ($p<0.001$). Eight of ten patients randomized to heparin recovered completely, and the remaining two had only mild neurological deficits. In the placebo group, only one patient had complete recovery, whereas three patients died[175]. The same research group also reported a retrospective study of 43 patients with cerebral venous sinus thrombosis associated with intracranial bleeding; 27 of these patients were treated with dose-adjusted heparin. The mortality rate in the heparin group was considerably lower than in the nonanticoagulated group[175]. In a more recent and slightly larger randomized study of cerebral venous sinus thrombosis (n=59), nadroparin (90 anti-Xa units/kg twice daily) was compared with placebo[176]. After 3 months of follow-up, 13% of the anticoagulation group patients and 21% of the placebo group patients had poor outcomes (RR reduction, 38%; p=NS). Two patients in the nadroparin group died *versus* 4 in the placebo group. Patients with intracranial bleeding were included, and no new symptomatic cerebral hemorrhages occurred in either group. From the results of these trials[175,176] and observational data, it appears that both UFH and LMWH are safe and probably effective in cerebral venous sinus thrombosis. Anticoagulation is recommended even in patients with hemorrhagic venous infarcts. No appropriate studies are available to address the optimal duration of anticoagulation. We recommend continuation of anticoagulation with an oral agent for 3 to 6 months. For patients who demonstrate continued neurological deterioration despite anticoagulation, local intrathrombus infusion of a thrombolytic agent has been reported[177] to produce effective clot dissolution, but further investigation of this option is needed.

While it is recommended to elevate the activated partial thromboplastin time (aPTT) up to twice the individual baseline, it is important to standardize aPTT ratios to heparin levels, as thromboplastins used to calibrate aPTT values vary significantly among local laboratories. Heparin should only be given as long as it takes to decide on the appropriate secondary prevention. Traditionally, contraindications for the treatment with heparin include large infarcts (e.g., more than 50% of MCA territory), uncontrollable arterial hypertension and advanced microvascular changes in the brain, although other studies negate these observations and emphasize to maintain aPTT within targeted values for safer use[178]. In the light of new results[168], reconsideration of the present therapeutic strategies for patients ineligible for thrombolysis within 3 hour time window is needed.

Hemodilution

Isovolemic hemodilution that lowers hemotocrit by 15% or more, results in reduction of blood viscosity and improvement of cerebral blood flow. Several large clinical trials of isovolemic hemodilution failed to demonstrate a decline in mortality or disability with treatment[179-181]. Hypervolemic hemodilution was assessed in small randomized trials with conflicting results. The clinical benefit of hemodilution therapy has not been established, and the possibility of brain edema has not been excluded.

Neuroprotection

There have been 11,000 patients in 65 neuroprotective trials involved. None of these showed convincing evidence for clinical and statistical benefit on its predefined primary endpoint and no compound has gained a product licence. A recent pooled analysis of the citicoline trial results suggests some effect on relevant outcome parameters, including MRI data[182].

Currently, there is no recommendation to treat patients with neuroprotective drugs after ischemic stroke.

Recommendations

1. Aspirin (100-300 mg *per* day) may be given within 48 h after ischemic stroke (Level I).
2. The administration of aspirin as and adjunctive therapy, within 24 hours of the use of thrombolytic agents, is not recommended (Level I).
3. Aspirin should not be used as a substitute for other acute interventions, especially intravenous administration of rt-PA for the treatment of acute ischemic stroke, if the thrombolytic agent and the settings are available (Level I).
4. Still, there is no recommendation for general use of heparin, low molecular weight heparin or heparinoids after ischemic stroke, although such statement may be reconsidered.
5. Full-dose heparin may be used when there are selected indications such as cardiac sources with a high risk of re-embolism, arterial dissection, cerebral venous sinus thrombosis, or high-grade arterial stenosis prior to surgery (Level IV).
6. Hemodilution therapy is not presently recommended for the management of patient with acute ischemic stroke (Level I).
7. Currently, there is no recommendation to treat stroke patients with neuroprotective substances (Level I) beyond the setting of clinical trials.

MANAGEMENT OF INTRACRANIAL AND SUBARACHNOID HEMORRHAGE

INCIDENCE, PROGNOSIS, AND MORTALITY

Intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) account for 10%-30% of all stroke admissions to hospital[183,184]. ICH alone accounts for 10%-17% of all strokes[185,186]. The incidence was found to be higher in Blacks, Hispanics and Asians compared with white population[185]. Primary ICH comprises 80%-85% and secondary 15%-20% of cases. Primary ICH is associated with hypertension in over 50%, and with cerebral amyloid angiopathy in 30% of cases[187]. Secondary causes of ICH are aneurysms, arteriovenous malformation, oral anticoagulant treatment, antithrombocytic therapy, coagulopathies, liver cirrhosis, neoplasms, trauma, vasculitis, moya-moya disease, sinus venous thrombosis, eclampsia, and cerebral endometriosis.

The classic presentation of ICH is sudden onset of a focal neurological deficit that progresses over minutes to hours with accompanying headache, nausea, vomiting, decreased consciousness and elevated blood pressure. Arterial hypertension is the most common risk factor for spontaneous ICH with a frequency of 70%-80%; other risk factors include age, ethnicity, cigarette smoking, alcohol consumption and low serum cholesterol lev-

els[188]. The risk of recurrent hemorrhage is as low as 2% *per* year when blood pressure is well controlled[189].

The 30-day mortality correlates with location and size of initial bleeding, and is found to be 35%-52%[190-193]. Only 20% of patients regain functional independence by 6 months[192,193]. Deep basal ganglial bleeding is often found in patients with hypertension, whereas lobar bleeding is more commonly seen in elderly patients with cerebral amyloid angiopathy[194]. About 40% occur in basal ganglia (caudate nucleus and putamen being the most common site), 30% in the thalamus, 20% are lobar, and 10% occur in the cerebellum and pons[190,195,196].

Deep hemorrhages are associated with high mortality rates; the mortality rate in patients with the initial volume >60 cm^3 is 93%, in cerebellar hemorrhages 75%, and in volumes <30 cm^3 23%, whereas in patients with lobar bleeding it is 71%, 57% and 7%, respectively[192]. Besides ICH volume and Glasgow Coma Score on admission, independent predictors of 30-day mortality are age >80 years, infratentorial origin of ICH and presence of intraventricular blood[197].

Additional intraventricular hemorrhage (IVH) is present in 36%-50% of patients with spontaneous ICH; the 30-day mortality rate is 43% in patients with IVH as compared with 9% in patients with only intraparenchymal blood[198].

EMERGENCY MANAGEMENT AND TREATMENT (GENERAL AND SPECIFIC) IMAGING

CT has been shown to have high sensitivity in ICH[199]. Hemorrhages that involve the putamen, globus pallidum, thalamus, internal capsule, periventricular white matter, pons and cerebellum, particularly in a patient with known hypertension, are often attributed to hypertensive small-vessel disease, and are often called "typical ICH"[200]. In these patients CT is sufficient and further imaging studies need not be required. In patients with clinical deterioration or IVH, repeat CT or MRI might be waranted. The appearance of ICH on MRI largely depends on the age of hematoma: hyperacute is isointense on T1 and hyperintense on T2 weighted images, so in acute stage the MR protocol should always include T2 and/or proton-density-weighted images; beyond 7 days the methemoglobin appears bright on T1 and T2 weighted images, and in the chronic stage a dark rim of hemosiderin is typical on MRI and is best seen on T2 weighted images[201].

If angiography is to be done, the timing will depend on the clinician's judgment. It depends on the clinical condition of the patient and the neurosurgeon's judgment of surgical emergency, if surgery is really needed. In patients with "typical ICH" but at a younger age with or without hypertension, further diagnostic work-up is needed including MRA, CTA and/or digital subtraction angiography (DSA). In patients with suspected non-hypertensive ICH, who might require emergency surgical evacuation, CTA is indicated as the fastest and most revealing technique[202]. The optimal technique to demonstrate low-flow vascular malformations such as cavernomas, hemorrhagic tumors and other vascular pathologies is MRI, and DSA for demonstrating high-flow vascular malformations such as AVMs and aneurysms. The most sensitive method to detect dural or cortical vein thrombosis which can present with ICH and venous infarction is MRI in combination with MR venography[203].

Recommendations

1. CT is indicated as an emergency method in all suspected ICH cases, the sensitivity between CT and MRI is almost equal if the MR protocol includes T2 and/or proton-density-weighted images (Level I).
2. Angiography should be considered for all patients without a clear cause of hemorrhage who are surgical candidates, particularly young, normotensive patients who are clinically stable. Angiography is not required for older hypertensive patients who have a hemorrhage in the basal ganglia, thalamus, cerebellum or brainstem, and in whom CT findings do not suggest a structural lesion (Level IV). Follow-up imaging is indicated in all other cases and should be performed within 4 weeks after the initial insult.
3. The underlying vascular pathology in non-hypertensive ICH should preferably be studied by CTA, or alternatively by MRA or DSA in cases where urgent surgical evacuation is indicated.
4. In cases where urgent surgical evacuation is not indicated, the underlying vascular pathology should be investigated by means of MRI for suspected cavernoma or cerebral amyloid angiopathy, CTA or MRA for dural sinus thromboses, and DSA for ruptured aneurysm or a pial or dural AVM (Level IV).

GENERAL AND SPECIFIC (MEDICAL AND SURGICAL) TREATMENT

All patients with ICH should be treated in stroke units if such units exist in the hospital or in ICU since treatment within specialized neurological intensive care units can decrease mortality to 28%-38% compared with the mortality rates of 25%-83% found if patients were treated in general intensive care units[204].

Management of ICH comprises:

1. General treatment
2. Prevention and treatment of complications (neurological – space-occupying edema, seizures or medical – DVT, aspiration, decubital ulcers)
3. Secondary prevention to reduce the incidence of early recurrence of ICH
4. Early rehabilitation
5. Specific therapy aimed to reduce the growth of hematoma

General treatment refers to clinical and instrumental monitoring in order to stabilize the patient in the acute phase. Neurological status is best monitored using validated neurological scales. General management comprises respiratory and cardiac monitoring, fluid balance and metabolic management, and control of blood pressure, blood glucose levels and body temperature. Prophylactic measures concern deep vein thrombosis (DVT), pulmonary embolism, aspiration pneumonia, decubital ulcers and infections[19-21]. Fluids such as 0.9% saline (about 1 mL/kg/h) should be given as the standard intravenous replacement fluid for patients with ICH. Free water given in the form of 0.45% saline or 5% dextrose in water can exacerbate cerebral edema and increase ICP. Systemic hypo-osmolality (<280 mmol/kg) should be aggressively treated with mannitol or 3% hypertonic saline[205].

MEDICAL TREATMENT

Blood pressure

Although there are no randomized trials to guide the management, it is generally in practice to correct the high blood pressure immediately to minimize the potential for hematoma expansion and rebleeding, and to maintain adequate cerebral perfusion pressure. The mean arterial pressure should be maintained at or below 130 mm Hg for patients with ICH and a history of hypertension[206-208]. Keeping the systolic blood pressure in acute ICH below 160 mm Hg and diastolic below 90 mm Hg leads to the growth of hematoma in 9% of patients as compared with 38% of patients in a study where the primary target was not blood pressure measurement[190,209]. In patients with known prior hypertension or signs of chronic hypertension, based on limited data, an upper limit of blood pressure should be 180/105 mm Hg, and in patients without known hypertension, the upper recommended limit is 160/95 mm Hg[22].

As the first line treatment to control hypertension, intravenous drugs with a short half-life can be used; labetalol (if available), nicardipin and enalapril are frequently recommended. Intravenous treatment of hypertension should always be accompanied by continuous blood pressure monitoring. Oral first line drugs include urapidil, labetalol and esmolol, if available, and in certain cases nitroprusside, furosemide, enalprilate; the administration of calcium antagonists (nicardipine) should be avoided because of their rapid hypotensive effect.

Seizures

The incidence of post-hemorrhagic seizures is higher (28%) as compared with ischemic stroke (6%)[210]. Seizures are associated with an increase in midline shift and neurological worsening (mainly caused by rebleeding) and more often occur in patients with lobar location and small sized ICH. In a prospective study, the prophylactic use of antiepileptic therapy in patients with lobar location led to a reduction in seizures[211]. Antiepileptic treatment in selected patients should be given for up to 1 month, after which therapy should be discontinued if there are no seizures[206-208]. Acute seizures should be treated with i.v. lorazepam (0.05-0.1 mg/kg), if available, followed by an i.v. loading dose of phenytoin (15-20 mg/kg), valproic acid (15-45 mg/kg) or phenobarbital (15-20 mg/kg).

Corticosteroids

Four small randomized trials of medical therapy for ICH have been conducted[212-214]; steroid *versus* placebo treatment[213,215], hemodilution *versus* best medical therapy, and glycerol *versus* placebo[213]. None of the 4 studies has shown any significant benefit for the three therapies. In the study testing steroids[212], patients who were treated with steroids were more likely to develop infections than those treated with placebo.

Prevention of DVT and pulmonary embolism (PE)

Graded compression stockings are effective in surgical patients; however, their efficacy has not been verified in hemorrhagic stroke. The administration of subcutaneous heparin and LMWH is usually withheld during the first few days after ICH and administered only in patients at a high risk of DVT or PE, at half of the normal dose[216]. It is recommended that a low dose of subcutaneous heparin or LMWH can be started on the second day after the onset of acute ICH since there is evidence for a lower incidence of PE in patients who received early heparin on day 2 as compared with patients who received their first heparin dose on day 4 or 10, and most important, the number of patients with ICH rebleeding was not increased[216].

Recommendations

1. All patients with ICH should be treated in stroke units or at ICU. Continuous cardiac monitoring is recommended in the first 48-72 hours of stroke onset (Level III)
2. Routine blood pressure lowering is not recommended. Treatment is recommended if blood pressure is elevated above the following levels, confirmed by repeat measurements. Recommended drugs for treatment are i.v. labetalol or urapidil, i.v. sodium nitroprusside or nitroglycerin and captopril *per os*. Calcium antagonists should best be avoided (Level IV).
   a) In patients with known arterial hypertension or ECG/retina signs of chronic hypertension: >180/105 mm Hg (treated blood pressure should be 170/100 mm Hg). Mean arterial pressure should be maintained at 125 mm Hg.
   b) In patients without known arterial hypertension: >160/95. Mean arterial pressure should be maintained at 110 mm Hg.
   c) A reduction by >20% of mean arterial pressure should be avoided.
3. General treatment is the same as for patients with ischemic stroke.
4. Early prophylactic treatment is not recommended for all patients, but may be considered for selected patients with lobar ICH. If they occur, acute seizures should be treated with i.v. lorazepam, if available, followed by an i.v. loading dose of phenytoin, valproic acid or phenobarbital. Antiepileptic treatment should be continued for 30 days (Level IV).
5. Corticosteroids are not recommended due to the possible side effects and higher rate of secondary infections (Level II).
6. Medical treatment for elevated ICP should be started if deterioration can be related to increasing edema (on CT or MRI). Short-term hyperventilation can be initiated intermittently for ICP crisis (Level IV).
7. Low-dose subcutaneous heparin or LMWH should be considered after 24 hours, especially in patients who are at a high risk of thromboembolism. Compression stockings are recommended (Level IV).
8. Early mobilization is recommended unless intracranial hypertension is present. Early rehabilitation is recommended; the same principles may be applied as in patients with ischemic stroke (Level IV).

SPECIFIC TREATMENT

Specific treatment is oriented to determination of bleeding mechanisms and the possibility of surgical treatment.

Recombinant activated factor VIIa (rFVIIa)

Recombinant activated factor VIIa (rFVIIa) is the only medical therapy so far that has shown benefit for patients with acute cerebral hemorrhage, given within four hours of clinical symptoms[195]. Hematoma volume increased more in the placebo group than in the rFVIIa groups. The mean increase was 29% in the placebo group, as compared with 16%, 14%, and 11% in the groups given 40 μg, 80 μg and 160 μg of rFVIIa *per* kilogram, respectively. Mortality at 90 days was 29% for patients who received placebo as compared with 18% in the three rFVIIa groups combined. Serious thromboembolic adverse events, mainly myocardial or cerebral infarction, occurred in 7% of rFVIIa treated patients as compared with 2% of those given placebo (nonsignificant).

Recombinant activated factor VIIa is recommended in patients with intracerebral hemorrhage within 3 hours, proven by CT scan in a dose of 80 μg *per* kilogram given as bolus i.v. in 2-5 minutes; rFVIIa should only be used in centers with neurological and neuroradiological 24-hour monitoring facility. Contraindications for treatment with rFVIIa are acute or recent (within 6 months) thromboembolic disease and patient in whom rFVIIa is not life-saving.

Recent reports have described the use of rFVIIa to speed the reversal of warfarin anticoagulation in patients with ICH; rFVIIa in doses ranging from 10 μg/kg to 90

μg/kg has been efficacious in the reversal of the effects of warfarin, primarily to expedite neurosurgical intervention[207,217].

Treatment of ICH related to oral anticoagulants (OAT)

ICH in patients on OAT has a poorer prognosis with larger bleeds and a higher case fatality than ICH in patients not receiving OAT[218]. The annual risk of ICH in patients who are on OAT is between 0.3% and 3.7% when the international normalized ratio (INR) is in the range between 2.0 and 4.5[219]. Every elevation of 0.5 INR units increases the risk of major bleedings (intracranial or fatal) by 1.4. If patients with ICH continue to receive OAT the risk of rebleeding is 54% as compared with 16% in patients who have discontinued receiving OAT in the first 7 days[218]. The rate of embolic events is low, even in high-risk patients, if OAT is interrupted for up to 10-14 days[220]. INR should be normalized urgently, which can be achieved by the administration of prothrombin complex concentrate (PCC), fresh-frozen plasma (FFP) or vitamin K. Considering when to resume therapeutic anticoagulation in patients who have suffered OAT-related ICH, the estimated existing risk of thromboembolism and the presumed pathophysiology of the ICH will determine the risk of hemorrhage recurrence[220,221]. Antiplatelet associated ICH seems to be a rare event in the primary prevention of cardiovascular events, as shown in a recently published meta-analysis[222]. The risk of ICH in patients who are on secondary prophylaxis with aspirin after ICH is not known.

SURGICAL THERAPY

HEMATOMA TREATMENT

The ideal goals of surgical treatment of ICH should be to remove as much blood clot as quickly as possible with the least amount of brain trauma from the surgery itself. If possible, surgery should also remove the underlying cause of ICH, such as an arteriovenous malformation, and prevent complications of ICH such as hydrocephalus and mass effect of the blood clot. Meta-analysis of 12 prospective randomized clinical trials in spontaneous ICH has shown an overall odds ratio for death of 0.85[22].

The STICH trial showed that surgical hematoma evacuation within 72 hours of onset does not improve outcome in comparison to a policy of initial medical management[196]. These results are consistent with those of a meta-analysis of all prior trials of surgical intervention for supratentorial ICH, which showed no benefits[223]. A small retrospective study of patients in STICH showed that the best results with emergency craniotomy were obtained in young individuals with large lobar hemorrhages rapidly deteriorating due to mass effect. A significant benefit of early surgery is seen is patients with GCS deterioration between 9 and 12 and/or the clot is superficial (=1 cm from the surface). Deep seated hematomas do not benefit from craniotomy.

Cerebellar hematoma may produce direct compression or hydrocephalus. Clot evacuation should be considered if there is neurological dysfunction or radiological evidence of obliteration of CSF spaces infratentorially and the clot is >2-3 cm in diameter[224].

ICH caused by AVM

Approximately 50% of all cerebral AVMs present with a hemorrhage; the risk of rebleeding in the first year is found to be 18%, however, the immediate short-term risk of rebleeding may be relatively low[225]. Unless a feeding artery aneurysm is identified as the bleeding source, the best approach is to stabilize the patient and perform surgery within 4-12 weeks of AVM bleeding. The management options include observation, embolization, surgical excision, and stereotactic radiotherapy. Combinations of these treatments afford the best results[226]. As for unruptured AVMs, there is an ongoing trial surgery *vs.* conservative treatment. It is considered that embolization is an optimal treatment modality for the treatment of the underlying vascular pathology including aneurysm, AVM and dural AVM but excluding cavernoma[227]. The goal is to eliminate or reduce the size of the AVM nidus, either as a sole treatment or as a preoperative method[228].

ICH caused by cavernous angiomas

The estimated annual bleed rate is 0.7% *per* year and *per* lesion[229]. DSA is often negative because cavernomas are part of the low-pressure system; angiography is positive in 10% of patients, the highest diagnostic sensitivity is yielded by T2 weighted MR sequences[229]. Up to 30% of cavernomas are associated with developmental venous anomalies; therefore all patients with a cavernoma should have a contrast MRI to rule out an accompanying developmental venous anomaly. Since it is difficult to predict the natural course of an individual caver-

noma, the treatment generally includes observation of patients with asymptomatic or inaccessible lesions, surgical excision of symptomatic and accessible lesions, and radiosurgery for progressively symptomatic but surgically inaccessible lesions (Level IV)[230].

Recommendations

1. Recombinant activated factor VII is recommended in patients with intracerebral hemorrhage within 4 hours, proven by CT scan, in a dose of 80 μg *per* kilogram in centers with neurological and neuroradiological 24-hour monitoring facility; however, a phase III trial is needed to confirm the beneficial effect of rFVII therefore, rFVII should not be used outside a phase III trial (Level I).
2. Consider craniotomy if there is deterioration in consciousness (from GCS level between 12 and 9 to =8), if the ICH is superficial (the clot is subcortical =1 cm from the surface and does not reach the deep basal ganglia), or if it is located in the cerebellum (Level III).
3. Deep seated hematomas do not benefit from craniotomy. Stereotactic aspiration may be considered especially if the mass effect is present (Level IV).
4. Management options for AVM include observation, embolization, surgical excision or focused radiotherapy. Combinations of these treatments afford the best results and have to be considered at the time of hemorrhage. Surgical treatment takes place within 2-3 months of the ictus if surgical excision is to be undertaken (Level IV).
5. In patients with an OAT-associated ICH and an INR >1.4 OAT should be discontinued, and the INR should be normalized with PCC or FFP. Intraveneous vitamin K should be added (Level IV).
6. After having re-checked the indication for anticoagulation OAT may be continued after 10-14 days, depending on the perceived risk of thromboembolic occlusion and ICH recurrence (Level IV).

SURGICAL TREATMENT OF ANEURYSM

Recommendations

1. Surgical clipping is recommended to reduce the rate of rebleeding after aneurysmal SAH (Level III)[231].
2. Early referral to specialized centers is recommended. Early surgery reduces the risk of recurrent hemorrhaging after SAH and is recommended for the good grade patient (Hunt and Hess 1 or 2) with uncomplicated aneurysm. For other clinical situations, either early or delayed surgery is recommended, depending on the specific clinical situation (Level II)[232,233].
3. Complete surgical obliteration of the aneurysm is recommended whenever possible, since wrapped or coated aneurysms or incompletely clipped aneurysms probably have an increased risk of recurrent hemorrhage (Level IV)[234].
4. Endovascular coil embolization is an option for treatment of ruptured and unruptured intracranial aneurysms[235]:
   a) for patients in good clinical condition if the aneurysm is considered suitable for surgical clipping and endovascular treatment; coiling is associated with a better outcome
   b) for patients in poor clinical grades, there is no reliable randomized evidence comparing the risks and benefits of coiling *versus* clipping, because coiling is less invasive than surgery, also in patients with poor clinical condition, coiling seems the preferred option

Measures of prevention of recurrent hemorrhage after SAH

Recommendations

1. Regulated bed rest or antihypertensive therapy are both frequently included in overall treatment of patients with SAH; these measures should be combined with other definitive measures to prevent recurrent hemorrhage (Level I)[236].
2. Carotid ligation is of indeterminate value in preventing rebleeding (Level I)[237].
3. Antifibrinolytic therapy to prevent recurrent hemorrhage is recommended in certain clinical situations, e.g., patients with a low risk of vasospasm and/or beneficial effect of delaying surgery (Level I). However, antifibrinolytic therapy has been associated with a higher rate of cerebral ischemia, resulting in no benefit in terms of overall outcome. Future studies are recommended to determine whether a combination of antifibrinolytic therapy with other treatments to reduce vasospasm will be beneficial[238].
4. Intraluminal coils and balloon-coils can promote aneurysmal thrombosis in a majority of cases, although long-term occlusion remains indeterminate[239].

Vasospasm after SAH

Cerebral vasospasm is a delayed narrowing of large capacity arteries at the base of the brain after SAH, often associated with radiographic or cerebral blood flow evidence of diminished perfusion in the distal territory of the affected artery. Angiographic vasospasm has a typical temporal course, with onset 3 to 5 days after the hemorrhage; maximal vasospasm is expected at 5 to 14 days, and gradual resolution over 2 to 4 weeks[240]. In about one half of cases, vasospasm is manifested by the occurrence of a delayed neurological ischemic deficit, which may resolve or progress to cerebral infarction (with acute or subacute development of focal or generalized symptoms)[241]. The incidence of angiographic vasospasm is over 50%, with symptomatic vasospasm in 32% of patients[214]. Therefore, TCD is a valuable tool for detection of vasospasm and timing of angiography.

Recommendations

1. Nimodipine is recommended to reduce poor outcome related to vasospasm, while complications and side effects of the drug are minimal (Level I)[242,243]. Other calcium antagonists given orally or intravenously are of uncertain value (Level I)[244,245].
2. Worse hypertension, hypervolemia and hemodilution are recommended for prevention and treatment of ischemic complications from vasospasm (Level III)[256,247].
3. Intracisternal fibrinolysis and antioxidant and anti-inflammatory agents are of uncertain value (Level III)[248].
4. Transluminal angioplasty is recommended for the treatment of vasospasm in patients in whom conventional therapy has failed (Level IV)[249,250].

Hyponatremia/Volume contraction

The reported incidence of hyponatremia following SAH ranges from 10% to 34%. It usually develops several days after the hemorrhage (day 3 to 15 after SAH) and is more common in patients with poor clinical grade[251]. Hyponatremia has been attributed to inadequate secretion of antidiuretic hormone. Hyponatremia lowers the level of consciousness, leads to muscular weakness, seizures and coma. Dehydration along with hypotension increases the risk of vasospasm[71]. Although the incidence of hyponatremia was not altered by the administration of large volumes of fluid or of fludrocortisone[72], hyponatremia is usually too mild to produce symptoms. Therefore, aggressive measures to correct hyponatremia appear unwarranted, especially if they lead to volume contraction.

Recommendations

1. Management of hyponatremia after SAH is recommended to emphasize the need to prevent volume contraction; management should include intravascular administration of isotonic fluids (Level III).
2. Hypotonic fluids should be avoided as they may contribute to hyponatremia; fluid restriction should not be instituted to treat hyponatremia (Level IV).

Complications of ICH

The early progression of the neurological deficit in many patients with ICH is frequently due to the ongoing bleeding and enlargement of the hematoma during the first few hours[190]. Enlargement of ICH may be seen up to 48 hours[254]. Brain edema after ICH is observed in the acute and subacute phase and may increase up to 14 days[255].

In patients with intraventricular hemorrhage (IVH), hydrocephalus is common and hydrocephalus is found to be an independent predictor of early mortality[256]. Hydrocephalus may occur with any type of intracranial hemorrhage. The outcome from ICH is much worse with IVH[257]. With SAH, hydrocephalus is often of the non-obstructive (communicating) type, while with the IVH or parenchymal hemorrhage more often non-communicating and with cerebellar hemorrhage it is always obstructive. Acute hydrocephalus (ventricular enlargement within 72 hours) is noted in 20%-27% of patients surviving the ictus of SAH, with a greater frequency among poor grade patients. Chronic ventriculomegaly occurs in 14%-60% of patients within 30 days from SAH[258]. Methods of treatment depend on the type of hydrocephalus. External drainage can be ventricular or *via* the lumbar route if it is a communicating type of hydrocephalus. Lumbar drainage is contraindicated with all types of obstructive hydrocephalus or if the etiology is in doubt. Internal drainage is achieved with a ventricular peritoneal or lumbar peritoneal shunt if the hydrocephalus is of communicating type. Antibiotic prophylaxis has been shown to be effective in CSF shunt operations[259]. Ventriculostomy has been associated with an increased rate of recurrent hemorrhage after SAH and may also be complicated by meningitis/ventriculitis[260,261].

Recommendation

External drainage for hydrocephalus can be ventricular or *via* the lumbar route if it is a communicating type of hydrocephalus (Level IV). Lumbar drainage is contraindicated.

PREVENTION AND TREATMENT OF POST-STROKE COMPLICATIONS

Approximately 25% of acute stroke patients can worsen during the first 24 to 48 hours. However, it is difficult to predict which patients will deteriorate[262]. The potential for preventable medical or neurological complications also means that these patients should be admitted to the hospital[95]. The goals of early post-treatment care after admission are to: 1) observe for changes in the patient's condition that might prompt initiation of medical or surgical interventions, 2) facilitate medical or surgical measures aimed at improving outcome after stroke, 3) begin measures to prevent subacute complications, 4) plan for long-term therapies to prevent recurrent stroke, and 5) start efforts to restore neurological function through rehabilitation and supportive care.

The most important medical complications[263,264] are pneumonia, urinary tract infections, malnutrition or volume depletion. Patients may also suffer from deep venous thrombosis and pulmonary embolism. Early supportive care and monitoring of physiological parameters may prevent such complications. This is best done in a dedicated stroke unit with experienced staff and early mobilization, since immobility may lead to infections, contractions and decubital ulcers. Both medical and neurological complications, stroke progression and recurrent stroke may lead to neurological deterioration (Table 11), requiring neuroimaging. The most important acute neurological complications of stroke are cerebral edema and increased intracranial pressure, which can lead to herniation or brainstem compression, seizure and hemorrhagic transformation of the infarction with or without formation of a hematoma.

Aspiration and pneumonia

One of the most important risks in the early phase after stroke is bacterial pneumonia[263,264], the majority being caused by aspiration[265], or may be hypostatic in origin due to poor coughing and immobilization. To reduce the risk of aspiration pneumonia, oral feeding should be withheld until the patient has demonstrated both intact swallowing with small amounts of water and intact coughing to command. In patients with reduced consciousness and in those with swallowing disturbances, nasogastric tube feeding is adequate for short-term enteral feeding, but a percutaneous enteral gastrostomy (PEG) should be inserted once it is clear that protracted enteral feeding will be required. A PEG is indi-

Cause	Action
«Evolving stroke» - worsening symptoms over 24 h or so.	Review diagnosis, early CT scan. Anticoagulation is not indicated
Raised intracranial pressure/herniation (edema), hydrocephalus	Repeat CT scan. Consider mannitol or neurosurgical opinion
Recurrent stroke	Seek «active» embolic source (e.g. cardiac, including endocarditis), alterna tive diagnosis, eg. vasculitis or fits. Oth erwise manage as first stroke
Hemorrhagic transformation of infarct	Stop aspirin or anticoagulants
Intercurrent infection	Check white cell count and inflammatory markers, review especially chest and urine
Drug adverse effect	Review
Metabolic disturbance	Check glucose, electrolytes (SIADH in 10% strokes)
Fitting (about 5% in acute phase)	Clinical diagnosis, need eyewitness ac count. Likely to recur if after the first 24 h. Oral sodium valproate, carbamazepine or i.m. phenobarbitone if no oral access.

Table 11. Neurological deterioration after stroke

cated when abnormal swallowing is predicted for periods longer than 1 month.

Nasogastric tube or PEG feeding through avoidance of swallowing may be helpful in prevention of aspiration pneumonia, but they do not completely reduce the risk, since reflux of liquid feed can itself promote aspiration. Hypostatic pneumonia may be prevented by frequent changes of the patient's position in bed and pulmonary physical therapy.

Urinary tract infection

Urinary tract infections are common and secondary sepsis can develop in approximately 5% of patients, incrasing the risk of death[266]. Urinary retention and/or incontinence are frequent in the early phase after stroke and will require insertion of a urine catheter or suprapubic catheter. Otherwise, incontinent patients should be managed with a condom catheter or 'pad and pants'. The majority of hospital-acquired urinary tract infections are associated with the use of indwelling catheters[267]. In non-stroke patients, suprapubic catheters are considered to carry a lower risk of infection[268], whereas intermittent catheterization has not been shown to have a reduced risk. Once urinary infection is diagnosed, appropriate antibiotics should be chosen. Prophylactic antibiotics should be avoided in order to diminish bacterial resistance.

Pulmonary embolism and deep vein thrombosis (DVT)

Pulmonary embolism accounts now, due to modern clinical practice and admission to a stroke unit, for approximately 10% of deaths after stroke, and the complication is detected in approximately 1% of persons who have had a stroke[269]. With prophylaxis, proximal DVT can be detected by plethysmography in one third to one half of patients who have sustained a moderately severe stroke[270]. The risk of DVT and pulmonary embolism can be reduced by early hydration and early mobilization. Although graded compression stockings are effective in preventing venous thromboembolism in surgical patients, their efficacy after stroke is unproven. Whilst subcutaneous heparin or LMWH reduces venous thromboembolism, the effect is counterbalanced by an increase in hemorrhagic complications. The prophylaxis with LMWHs and heparinoids appears to decrease the occurrence of DVT as compared to standard unfractionated heparin[271], and is reasonable in patients at a particularly high risk of DVT or pulmonary embolism. Aspirin may also be effective for patients who have contraindications for the use of anticoagulants[272,273].

Decubital ulcer

Frequent turning of immobilized patients is useful for prevention of decubital ulcers. The skin of the incontinent patient must be kept dry. For patients at a particularly high risk, an air-filled or fluid-filled mattress system should be used. If decubital ulcers do not respond to conservative therapy, antibiotic therapy may be justified for several days, preceding definitive surgical debridement.

Seizures

The reported frequency of seizures during the first days after stroke ranges from 4% to 43% depending on study design[274]. The true risk of seizures appears to be towards the lower end of the estimates. Seizures are most likely to occur within 24 hours of stroke and are usually partial with or without secondary generalization. Recurrent seizures develop in approximately 20%-80% of patients. Intermittent seizures seem not to alter the overall prognosis after stroke. However, status epilepticum can be life-threatening, but fortunately, it is uncommon. There is no evidence that prophylactic anticonvulsive treatment is beneficial. There are few data concerning the efficacy of anticonvulsants in the treatment of stroke patients who have experienced seizures; thus, recommendations are based on the established management of seizures that may complicate any acute neurological illness.

Agitation

Agitation and confusion are rarely caused by stroke, but are more frequently a symptom of other complications such as fever, volume depletion, infection or prior drug or alcohol abuse. Therefore, appropriate treatment of the underlying cause must precede any type of sedation or antipsychotic treatment.

Hemorrhagic transformation

There is considerable information on the natural rate of early hemorrhagic transformation of ischemic stroke. Some studies suggest that almost all infarctions have some element of petechial hemorrhage. Using CT, one prospective study estimated that approximately 5% of infarctions would spontaneously develop symptomatic

hemorrhagic transformation or frank hematomas[275]. The location, size and etiology of stroke can influence the development of this complication. Further information on the influence of hemorrhagic transformation on outcome after stroke is needed. Small asymptomatic petechiae are much less important than hematomas, which can be associated with neurological decline. The use of all antithrombotics, especially anticoagulants and thrombolytic agents, increases the likelihood of serious hemorrhagic transformation. The early use of aspirin also is associated with a small increase in the risk of clinically detectable hemorrhage. The management of patients with hemorrhagic infarction depends on the amount of bleeding and its symptoms. In Table 9, the management of symptomatic intracranial hemorrhages after thrombolysis is listed.

Recommendations

1. Low-dose subcutaneous heparin or LMWHs should only be considered for patients at a high risk of DVT or pulmonary embolism (Level II).
2. The incidence of venous thromboembolism may be reduced through early rehydration and mobilization and graded compression stockings (Level IV).
3. Infections after stroke should be treated with appropriate antibiotics.
4. Aspiration pneumonia may not be prevented by nasogastric feeding (Level IV).
5. Early mobilization is helpful to prevent numerous complications after stroke including aspiration pneumonia, DVT and decubital ulcers (Level IV).
6. Administration of anticonvulsants to prevent recurrent seizures is strongly recommended (Level III).
7. Prophylactic administration of anticonvulsants to patients with recent stroke who have not had seizures is not recommended (Level IV).

Brain edema and elevated ICP

Brain edema and increased intracranial pressure largely occur with occlusions of major intracranial arteries that lead to multilobar infarctions[276], or may be the consequence of parenchymal hemorrhages. The edema occurs during the first 24-48 h after stroke onset and peaks at 3-5 days after stroke. It is the main reason for early[277,278] and late[278] clinical deterioration, not only for impairment of the level of consciousness and brain herniation, but also for impairment of other neurological functions such as motor strength or speech. Less than 10%-20% of patients develop clinically significant edema that could warrant medical intervention. It is a problem within the first 24 hours in patients with cerebellar infarctions, or in younger patients with complete MCA infarction in whom brain edema and elevated ICP may lead to herniation within 2-4 days after the onset of symptoms, and to death in about 80% of cases with standard treatment[276,279,280]. Increased ICP also can result from acute hydrocephalus secondary to the obstruction of CSF pathways by a large cerebellar lesion.

The goals of management of brain edema are to: 1) reduce ICP, 2) maintain adequate cerebral perfusion to avoid worsening of brain ischemia, and 3) prevent secondary brain injury from herniation. Factors that exacerbate the raised intracranial pressure (e.g., hypoxia, hypercarbia, hyperthermia, hyperglycemia and high blood pressure) should be treated. Avoidance of noxious stimuli, pain relief, oxygenation and normalization of body temperature are recommended. Hypotonic and glucose-containing solutions should be avoided as replacement fluids.

Medical therapy

The basic management of elevated ICP following stroke includes 30° upright position and patients should not be turned to either side during the first 24 h. The level of sedation must be controlled and adjusted if necessary to avoid pain and anxiety. Body temperature should be normalized.

Although strong evidence is lacking[281,282], osmotherapy with 10% glycerol usually given intravenously (4x250 mL of 10% glycerol over 30-60 min) or intravenous mannitol 25-50 g every 3-6 h is the first medical treatment to be used if clinical and/or radiological signs of space-occupying edema are obtained. It should not be given for longer than 2 days or in emergency situations (for example, decompensated ICP). Mannitol is cleared by the kidney and acts as an osmotic diuretic. Electrolytic disturbance and hypovolemia are complications of osmotherapy with mannitol. During osmotherapy, plasma osmolality should not exceed 330 mOsm/kg. Short-term increases of osmolality seem to be more effective in reducing ICP compared with continuous high osmolality. Osmotherapy is only effective for 48-72 h. Hypotonic and glucose-containing solutions should be avoided as replacement fluids.

Hypertonic saline solutions given intravenously[283] are probably similarly effective, although data at present available are not definitive[284].

Dexamethasone and corticosteroids are not useful for brain edema treatment after stroke[285], and they increase the risk of infections.

If ICP monitoring is available, cerebral perfusion pressure should be kept >70 mm Hg[286,287]. ICP monitoring, with intraventricular, intraparenchymatous or epidural catheters is essential, particularly in comatose or sedated patients where clinical assessment is not feasible. ICP monitoring reduces the need of neuroradiological examinations and allows for evaluation of the effectiveness of diverse therapeutic approaches, but is strictly limited to intensive care stroke units. The value of continuous ICP monitoring in this population has not yet been established, although the results can help predict the patients's outcome and guide the choice of therapies[288].

In agitated patients tranquilizers are recommended. Short-acting barbiturates such as thiopental given as a bolus can quickly and significantly reduce ICP, but the effect is short lived and can only be used to treat an acute crisis, e.g., prior to operation. Barbiturate treatment requires ICP and EEG monitoring and careful monitoring of hemodynamic parameters, since a significant blood pressure drop may occur. ICP monitoring is also required when Tris (hydroxy-methyl) aminomethane buffer solution is used after osmotherapy and barbiturate failure[280]. Analgesics may be added if necessary.

Volume loading by vasopressor induced hypertension may be attempted in case of severely compromised cerebral perfusion pressure, but hemodynamic monitoring and intensive care facilities are required.

Hyperventilation

Hyperventilation is an emergency measure that acts almost immediately; a PCO_2 reduction by 5 to 10 mm Hg can lower ICP by 25%-30%[289]. Hyperventilation is a temporizing measure and should be supplemented by another intervention to definitively control brain edema and ICP. Maintaining adequate brain perfusion is necessary since hyperventilation can lead to vasoconstriction that might aggravate ischemia.

Hypothermia

As previously mentioned, hypothermia has been shown to be neuroprotective after experimental global and focal hypoxic brain injury[139], and after cardiac arrest[290,291]. Mild hypothermia (i.e. brain temperature between 32 and 33 °C) reduces the case fatality rate of patients with severe MCA infarcts, but causes a number of severe side effects which may be encountered during therapy over several days[292]. The number of studied patients is still too small to draw any decisive conclusions, but the method has been tested prospectively in randomized trials. The problem is recurrent ICP crisis, which was almost exclusively found during re-warming[280]. Moreover, in a comparative trial, hypothermia had more severe side effects than decompressive surgery for malignant MCA infarction[293].

Muscle relaxants

Neuromuscular paralysis in combination with adequate sedation can reduce elevated ICP by preventing increases in intrathoracic and venous pressure associated with coughing, straining, suctioning, or "bucking" the ventilator (Level III). Nondepolarizing agents such as vecuronium or pancuronium with only minor histamine liberation and ganglion-blocking effects are preferred in this situation. Patients with critically elevated ICP should be pretreated with a bolus of a muscle relaxant before airway suctioning.

Decompressive surgery

Space-occupying hemispheric infarction, the so-called malignant MCA infarction, has a high mortality and morbidity even with optimal conservative treatment. Hemicraniectomy has been used to control ICP and prevent herniation in patients with very large infarctions of the cerebral hemisphere.

Malignant MCA infarction. Hemicraniectomy to remove the skull, temporal lobe resection has been used to relieve dural compression in order to treat malignant brain edema, thus allowing expansion of the edematous tissue to reduce ICP, to increase perfusion pressure, and to preserve cerebral blood flow by preventing further compression of the collateral vessels. If hydrocephalus is present, CSF drainage *via* an intraventricular catheter can rapidly lower ICP. In a prospective case series, surgical, decompressive therapy in hemispheric space-occupying infarction lowered mortality from 80% down to 30% without increasing the rate of severely disabled survivors[216,279,295]. Early decompressive surgery within the first 24 h after stroke onset can reduce mortality even more markedly[295].

Cerebellar infarction. Ventriculostomy and suboccipital craniectomy, especially in concert with aggres-

sive medical therapies, appear to be effective in relieving hydrocephalus and brainstem compression caused by large cerebellar infarctions, although the scientific basis for this is no 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 rate can be lowered to less than 30% if decompressive surgery is performed[296,297]. Decompressive surgery of posterior fossa is significantly superior to ventriculostomy[152]. Like in space-occupying supratentorial infarction, the operation should be performed before the signs of herniation set in. The prognosis among survivors is good, even if they were comatose when the operation was performed. These were the results of open, small- or medium-sized case series, one of them being prospective[279], and the remainder were mostly retrospective, while data from a controlled, randomized trial are lacking.

Recommendations

1. Corticosteroids are not recommended in the management of brain edema (Level I).
2. Osmotherapy is recommended for patients whose condition is deteriorating secondary to increased ICP, including those with herniation syndromes (Level IV).
3. Hyperventilation at a constant tidal volume is recommended to lower ICP (Level III).
4. Muscle relaxants in combination with sedation are recommended to reduce increased ICP by preventing increases in intrathoracic and venous pressure associated with coughing, straining, suction or "bucking" the ventilator (Level III).
5. External ventricular drainage or ventriculostomy can be used to treat increased ICP due to hydrocephlus (Level III).
6. Ventriculostomy or surgical decompression and evacuation of large cerebellar infarctions that compress the brainstem and cause hydrocephalus are justified (Level III).
7. 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 for independent life (Level III).

REHABILITATION

Early stroke rehabilitation is a key consideration in acute stroke management. As mentioned before, the Stroke Unit Trialists Collaboration[298] in a systematic review of 29 clinical trials showed that interdisciplinary stroke rehabilitation therapeutic environment accounted for much of the success of stroke units with the success of stroke units to be more a consequence of stroke rehabilitation therapies. Forty per cent of stroke survivors remain dependent upon others for their activities of daily living, therefore they need active rehabilitation services. Some studies have suggested that early physical therapy helps in functional improvement and reduces the number of patients who are left dependent after stroke[299]. The principal aims of stroke rehabilitation should be to prevent contractures and embolism, optimize treatment associated with specific medical problems, and provide psychological support to patients and their families.

Early rehabilitation

Rehabilitation of a stroke victim is started as soon as the victim is clinically stable. The intensity of the actual rehabilitation program depends on the status of the patient and the degree of disability. In unconscious patients or patients incapable of active training, passive methods may be used to prevent contractions and joint pain as well as distress for the patient when active movement is restarted after immobilization. Passive rehabilitation measures minimize the risk of decubital ulcers and pneumonia. All joints on the paralyzed side are moved through the full range of motion several times a day (at least 3-4 times). Co-operative patients are encouraged to take an active part in the rehabilitation program. Prolonged immobilization and hemiplegia carry the risk of deep venous thrombosis and pulmonary embolism. After 2 or 3 days, most patients who are alert can be moved out of bed with safety and placed in a wheelchair for a good part of the day.

Acute stroke rehabilitation

The role of rehabilitative efforts has been recognized as being essential in the acute stroke management. The beneficial effects of rehabilitation at stroke units have been well documented[300,301]. Treatment of acute stroke patients in stroke units has been shown to reduce mortality, length of hospital stay, discharge rate to nursing home and costs[302]. Functional recovery was significantly greater and more rapid in a stroke unit compared with general wards[301]. Treatment in stroke units has increased the proportion of patients able to live at home after stroke[303]. Treatment in dedicated stroke rehabilitation

wards is based on multidisciplinary teamwork consisting of a physician, physiotherapist, speech therapist, occupational therapist, neuropsychologist, social worker and nurse[298]. In such a unit, there is a motivating and encouraging attitude that maintains the patient's desire to improve. Important is the milieu of an 'enriched environment', where patients feel comfortable, and which supports the patient's efforts and encourages him/her to practise even beyond working hours[304]. Elderly stroke patients also benefit from the well-organized stroke management[302,305].

Rehabilitation programs

After the initial stroke phase has passed, the patient should be assessed for the degree of disability. The extent and distribution of motor weakness and the accompanying sensory and proprioceptive deficits should be noted in detail. The assessment should include evaluation of intellectual impairment, especially specific cognitive deficits such as aphasia, apraxia, agnosia, disorders of memory and attention, and the broad range of emotional distress and motivational disturbances. After evaluation of the patient's degree of disability, a rehabilitation program will be tailored according to the individual needs, potential for recovery and facilities. Patients with mild neurological impairments require only limited training in basic self-care, ambulation and functional communication. The recommendations for their management are mostly based on clinical experience and expert consensus. Compelling evidence on the basis of randomized clinical data is not availale for such patients or for patients who have more severe impairments or multiple medical comorbidities. These patients are best managed in a subacute rehabilitation unit or should be admitted to a specialized rehabilitation hospital. In these settings, rehabilitation should be a full-day work. For patients with complex stroke syndromes, rehabilitation at a specialized ward or hospital is more efficient and cost effective[306].

When the patient is transferred to a rehabilitation hospital, it is of utmost importance that the complete documentation of the patient's progress is transferred to the rehabilitation hospital[305]. After institutional rehabilitation, the rehabilitation program can be taken over by an outpatient rehabilitation clinic. This ensures smooth transfer of the patient to the next rehabilitation step back to normal. The length of the rehabilitation period in the acute stage depends on the stroke severity and locally available stroke rehabilitation services. Under usual circumstances, rehabilitation following the acute phase of ischemic stroke should not last for more than 6-12 weeks and rarely more than 24 weeks.

Brain research has produced new information that gives an encouraging insight into rehabilitation after stroke. Recent reports on the "forced use" of the affected limb showed promising results. The method is based on developing muscle strength and increasing the range of movements with plentiful repetition and enhanced resistance training of the affected limb. It is thought that these techniques are based on the principles of plasticity in the adult human brain which allow for reorganization of nervous networks, and this plasticity can be activated by repeated task-specific training. These restorative programs are focused on the functional improvement of the upper extremity[307,308] or on the recovery of gait[309,310], offering a promising tool for the treatment of stroke patients with residual disability.

The fastest recovery of neurological deficit occurs during the first 3 months after the onset of symptoms. Active rehabilitation, however, should be administered as long as objective improvement in the neurological function is observed.

In addition to national organizations involved in providing information to stroke survivors, the role of locally based self-help groups is important in supporting stroke patients and their caregivers. There is a low level of service provision especially for older stroke survivors living in the community, and more rehabilitation and co-operation with primary and secondary health care would be requird to ensure an optimal long-term outcome. Since most elderly patients prefer to stay at home, community care has acquired a greater relevance. An important requirement of good health care and social services for elderly people living in the community would be flexibility of service provision, implying the need of patient assessment before admission to the appropriate service. Well-integrated social and medical care with case management programs may be one way to reduce admission to institutions and prevent functional decline in the elderly[311].

Home treatment in the chronic phase of stroke

Supporting the patient in his/her social environment is important. Keeping up social contacts is perhaps something that offers the best opportunity to influence the patient's quality of life. Every chronic stroke patient with

a marked disability should have regular contact with family physician who can encourage the patient, notice possible impairment of clinical state, and take care of secondary prevention.

With focused rehabilitation programs, stroke patients can become ambulatory and largely independent. Of major importance is that the majority of survivors are able to live at home and do not require nursing home care[306]. The evidence that such results can be achieved with systematic stroke management is identical from University Hospitals of Umeå, Sweden[312], Copenhagen, Denmark[313], Kuopio, Finland[314] and Trondheim, Norway[300].

Recommendations

1. Every patient should have access to evaluation for rehabilitation.
2. In patients with a clear indication for rehabilitation, treatment should be initiated early after stroke (Level I). Disabled patients should have access to structured care including institutional care.
3. Rehabilitation should be provided by a multidisciplinary team in a stroke unit (Level I).
4. 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 (Level IV).
5. Patients with chronic symptomatic stroke should be supported in their social environment. This includes access to a family physician, evaluation of outpatient rehabilitation services, secondary prevention and support in psychosocial functioning (Level II).

PART III
PRIMARY AND SECONDARY PREVENTION

PRIMARY PREVENTION

Primary prevention is aimed at reducing the risk of stroke in asymptomatic people. Lifestyle and several medical conditions have been associated with an increased risk of stroke, therefore they are identified as risk factors for stroke. Modification of risk factors for stroke is known to decrease the incidence of stroke in asymptomatic people, and they are used in primary prevention of stroke.

Diet

Modifying diet reduces the risk of stroke. Available evidence supports the use of diets high in non-hydrogenated unsaturated fats, whole grains, fruit and vegetables and adequate omega-3 fatty acids[315]. Eating fish once a month may also be associated with a decreased risk of stroke in men[316]. Such a diet should be low in salt and saturated fat.

A report from the Framingham Study[317] indicates that increased daily consumption of fruits and vegetables may decrease the risk of stroke, including hemorrhagic stroke. Increased fruit and vegetable intake is associated with a reduced risk of stroke. In a meta-analysis of eight studies, consisting of nine independent cohorts, including 257551 individuals (4917 stroke events) with an average follow-up of 13 years, the relative risk of stroke was 0.74 (95% CI 0.69–0.79) for those with more than five servings of fruit and vegetables *per* day[318].

Fruit and vegetables are rich in many health promoting nutrients and food compounds including antioxidants such as vitamin C and folate, potassium, phytochemicals, dietary fiber, and plant proteins that have been inversely related to high blood pressure and stroke[319-323].

It is likely that the combination of nutrients and compounds in foods has greater health benefits than the individual nutrient alone[324].

Physical activity

Substantial evidence exists that physical activity exerts a beneficial effect on multiple risk factors for stroke and that physical activity is inversely related to the risk of stroke[325,326]. A prospective cohort study of male participants in the Physician Health Study revealed that vigorous exercise is associated with a decreased risk of stroke. However, it seems that this association is mediated through the beneficial effects on body weight, blood pressure, serum cholesterol and glucose tolerance. Apart from these indirect effects, physical activity has shown no direct influence on stroke incidence.

In a review of the existing studies on physical activity and stroke, overall moderately or highly active individuals had a lower risk of stroke incidence or mortality than the low-activity individuals: moderately active men and women had a risk lower by 20%, and those who were highly active by 27%[327].

Obesity

Obesity, defined as a body mass index (BMI) of >30 kg/m^2, has been established as an independent risk factor for coronary heart disease (CHD) and premature mortality[328-330]. However, the relationship of obesity to stroke is complex. Obesity is strongly related to several major risk factors, including hypertension, diabetes, and dyslipidemia[331,332]. Studies documenting the specific impact of obesity on stroke are variable[334-338]. In men, findings from the Physicians' Health Study have shown that an increasing BMI is associated with a steady increase in ischemic stroke, independently of the effects of hypertension, diabetes, and cholesterol[339]. Among women, data are inconsistent, with some positive[340] and others with no association[336,338,340,341]. Several studies have suggested that abdominal obesity rather than general obesity is more related to stroke risk[342,343]. Clinically, abdominal obesity is defined by a waist circumference >102 cm in men and 88 cm in women. For stroke, a significant and independent association between abdominal obesity and ischemic stroke was found in all racial/ethnic groups in the Northern Manhattan Study[342]. However, no study has demonstrated that weight reduction will reduce stroke recurrence. Losing weight, however, significantly improves blood pressure, fasting glucose values, serum lipids, and physical endurance[344]. Because obesity is a contributing factor to other risk factors associated with recurrent stroke, promoting weight loss and maintenance of a healthy weight is a high priority. Diets rich in fruits and vegetables, such as the Mediterranean diet, can help with weight control and have been shown to reduce the risk of stroke, MI, and death[345,346].

Cigarette smoking

Approximately 25% of adults are active cigarette smokers, but figures differ according to countries, age categories, education and gender[347]. Cohort studies have shown cigarette smoking to be an independent risk factor for ischemic stroke in both men and women, and there is strong and convincing evidence that cigarette smoking is a major independent risk factor for ischemic stroke[348-355]. On the other hand, nearly 90% of non-smokers have detectable levels of serum nicotine[356]. There is growing evidence that exposure to environmental tobacco smoke (or passive smoke) increases the risk of stroke[357-359]. Because of the high prevalence of environmental exposure, a small increase in the RR of stroke due to environmental tobacco smoke may be associated with a great attributable risk in the community[356]. These data make cigarette smoking an important risk factor for stroke in the population.

The risk associated with smoking is present at all ages, in both sexes, and among different racial/ethnic groups. The risks are directly dependent on the consumption of cigarettes and may be as high as 6-fold compared with non-smokers. In subjects who stopped smoking the risk of stroke decreases after quitting and the elevated risk disappears after 5 years[354,360,361].

Alcohol consumption

There is strong evidence that chronic alcoholism and heavy drinking are risk factors for all stroke subtypes[362-366]. However, the association between alcohol consumption and stroke is complex and may differ between Caucasian and other populations, e.g., Japanese people. In the Honolulu Heart Program, heavy drinkers had a threefold risk of hemorrhagic stroke (subarachnoid hemorrhage or intracerebral hemorrhage) found in non-drinkers[367]. For ischemic stroke, studies have demonstrated an association between alcohol and stroke, ranging from a definite independent effect to no effect. Most studies have suggested a J-shaped association between alcohol and ischemic stroke, with a protective effect in light or moderate drinkers and an elevated stroke risk with heavy alcohol consumption[368-376].

In a meta-analysis of 35 observational studies of the association between alcohol and stroke, alcohol consumption was categorized into 0, <1, 1 to 2, 2 to 5, >5 drinks *per* day; an average drink contained about 12 g or 15 mL of alcohol. Compared with nondrinkers, those who consumed >5 drinks *per* day had a 69% increased stroke risk[377]. A case-control study suggested that moderate alcohol consumption (up to two drinks of liquor, two cans of beer, or two glasses of wine *per* day) would decrease the risk of ischemic stroke. On the contrary, heavy alcohol consumption is associated with an increased risk of both ischemic and hemorrhagic stroke[372]. A case-control study in a multiethnic population suggested that moderate consumption (up to 2 drinks of spirits, 2 cans of beer or 2 glasses of wine, equivalent to 20-30 g of ethyl alcohol *per* day) was associated with a decreased risk of ischemic stroke, while heavy alcohol consumption was associated with an increased risk of ischemic and hemorrhagic stroke[377]. A recent meta-analysis has given similar results by showing that heavy alcohol drinking (more

than 60 g/day) increases the RR of stroke, while light or moderate alcohol consumption may be protective against total and ischemic stroke. A consumption of less than 12 g of alcohol *per* day was associated with a reduced risk of total stroke (RR=0.83) and ischemic stroke (RR=0.80) and a moderate consumption of alcohol (12-24 g/day) was associated with a reduced RR of ischemic stroke (0.72)[378].

The mechanism for reduced risk of ischemic stroke with light to moderate alcohol consumption may be related to an increase in HDL[379-381] and lower plasma fibrinogen concentration[382,383]. The mechanisms for higher stroke risk in heavy alcohol consumers include alcohol-induced hypertension, hypercoagulable state, reduced cerebral blood flow, and atrial fibrillation[375,384,385]. Also, the brain of the subjects that heavily consume alcohol is more vulnerable because of an increase in the presence of brain atrophy[386,387].

Stress

Stress reaction enhances platelet aggregation. It also activates the renin-angiotensin system and production of angiotensin II leading to a rise in arterial blood pressure. Stress causes a higher incidence of cardiovascular and cerebrovascular disorders[388,389].

Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men[390]. However, only scarce data exist about direct connection of stress and stroke[6,391-396]. Most of these studies are difficult to compare due to different population, different design and due to difficulties in the definition of stress. However, data from these studies mainly indicate that stress is associated with a higher incidence of hemorrhagic stroke in particular.

Oral contraceptives

The risk of stroke in general and of ischemic stroke in users of oral contraceptives (OCs) is increased, and is particularly increased when using OCs with a higher estrogen content[397]. Whether low dose OCs carry a risk is still being debated, since available data indicate no increase in the risk in the USA[398], a slightly increased risk in Europe, and a three-fold risk in Africa, Asia and Latin America[399]. In a WHO study conducted in the developing countries, the risk of cerebral hemorrhage was significantly increased among OC users in general[400]. The risk was proven higher with high-dose OCs, it significantly increased with age ($\geq$35 years) and other associated risk factors such as hypertension and smoking. OC use is also associated with a small increase in the risk of SAH. This increase is marginal with low-estrogen preparations but is strongly increased with concomitant hypertension[400].

Postmenopausal estrogen replacement therapy

Stroke rates rise rapidly in women after menopause. There are numerous observational studies of the benefits of postmenopausal hormone replacement therapy relative to stroke risk[401,402]. In an analysis based on a 16-year follow-up of 59,337 postmenopausal women participating in the Nurses' Health Study, there was only a weak association between stroke risk and estrogen replacement[403]. According to the HERS II trial, hormone replacement in healthy postmenopausal women is associated with an increased risk of ischemic stroke[404], and therefore is **not** recommended.

Illegal drugs

The use of cocaine, especially alkaloidal forms ("crack") has been associated with a consistent increase in the risk of both ischemic and hemorrhagic stroke[405].

Hypertension

Hypertension is the most prevalent and modifiable risk factor for stroke, and its treatment substantially reduces the risk of stroke[406]. A meta-analysis of 14 randomized trials has shown that a decrease of diastolic blood pressure by merely 5-6 mm Hg in hypertensive patients equals a 42% reduction in stroke incidence[407].

The Systolic Hypertension in the Elderly Program (SHEP) has shown that the management of isolated systolic hypertension (greater than 160 mm Hg) in patients older than 60 years reduces the total incidence of stroke by 36% and of inracerebral hemorrhage alone by 50%[408].

Protection largely depends on the intensity of treatment and magnitude by which blood pressure is lowered[409]. Throughout middle and older age, blood pressure is strongly and directly related to vascular and overall mortality without any evidence of a threshold down to at least 115/75 mm Hg[410].

Most studies comparing different hypotensive drugs have not suggested that any class is superior[409,410]. However, the LIFE trial found that losartan (50-100 mg), an

angiotensin receptor blocker (ARB), reduced first stroke more than the beta-blocker (BB) atenolol in 9,193 patients, although a similar blood pressure reduction was obtained in both groups[411]. In the ALLHAT study, a thiazide diuretic, chlorthalidone, was superior to a calcium channel blocker (CCB) amlodipine, alpha-receptor antagonist doxazosin, and angiotensin-converting enzyme inhibitor (ACEI) lisinopril in preventing one or more major forms of vascular events including stroke[412].

The desirable blood pressure level in primary stroke prevention is not definitively established, but most authorities suggest levels below 140/90 mm Hg, and in diabetic patients even lower (see below). The management of hypertension begins with lifestyle modifications because blood pressure reductions have been associated with weight loss; consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; and limited alcohol consumption[413]. However, many patients will need pharmacotheapy to achieve desirable blood pressure levels. The choice of antihypertensive therapy should be tailored using the AB/CD rule for each patient depending on his/her age, and the presence of other comorbid conditions[414,415]. Most patients with high blood pressure will need multiple drug therapy to achieve levels below 140/90 mm Hg[409,410,413].

Diabetes mellitus (DM)

Although DM is recognized as an independent risk factor for ischemic stroke, it is not established whether strict control of blood glucose can be a factor in stroke prevention. In fact, in patients with type 2 DM, intensive sulphonylurea and/or insulin therapy ameliorated microvascular systemic complications, but not macrovascular ones such as stroke[416]. However, there are many other good reasons to treat DM appropriately in patients at risk of stroke. Blood pressure should be lowered more aggressively in diabetic patients to achieve levels below 135/80 mm Hg[417]. It seems that treatment with ACE inhibitors or angiotensin receptor agonists (ARA) could delay the onset of DM[411,418].

Hypercholesterolemia

The relationship between serum cholesterol levels and CHD has been well established, but its relationship with stroke is less clear. A meta-analysis did not find any strong association between serum cholesterol levels and stroke, but it did not differentiate between ischemic and hemorrhagic stroke[419]. Recent studies have found that ischemic stroke is positively associated with cholesterol levels, while hemorrhagic stroke is not[420,421]. Large studies have demonstrated that statins can decrease the risk of stroke for patients with CHD: 24% relative risk reduction of stroke with simvastatin therapy in the 4S study [422]; 19% relative risk reduction of stroke with pravastatin therapy in the LIPID study[423]; and 32% relative risk reduction of stroke in the CARE study [424]. Two trials assessed the effect of statins (lovastatin and pravastatin) in subjects with moderately elevated cholesterol levels and no history of vascular events: stroke was not reported in the lovastatin trial, and pravastatin reduced stroke nonsignificantly in men by 11%[425,426]. Two other primary or combined primary/secondary prevention trials were unable to show a reduction in stroke rate in persons treated with pravastatin *versus* placebo[427,428]. In the Heart Protection Study, 20,536 UK adults aged 40-80 years with CHD, other occlusive arterial disease or DM were randomly allocated to receive 40 mg simvastatin daily or placebo. There was a highly significant reduction in nonfatal or fatal strokes (4.3% *vs.* 5.7%; $p<0.0001$). The proportional reduction in the event rate was similar and significant in each subcategory of study subjects, including those without diagnosed CHD who had cerebrovascular disease and even those who presented with low-density lipoprotein cholesterol below 3.0 mmol/L, or total cholesterol below 5.0 mmol/L[429].

Antithrombotic drugs

Many studies have assessed aspirin in the primary prevention of vascular events[430-436]. In all these trials ASA was shown to reduce the risk of CHD and MI but not of stroke. Also, a meta-analysis of the first 5 trials comparing ASA with no ASA included 52,251 subjects[436]. While ASA reduced the risk of MI (RR: 0.74; 95% CI: 0.68-0.82), it had no effect on stroke (RR: 1.08; 95% CI: 0.95-1.24). Taken together, all these studies as well as the meta-analysis do not provide evidence for the use of ASA in primary prevention of stroke. However, since ASA reduces the risk of CHD and MI, it can be recommended in subjects with vascular risk factors[435,437].

No data are available on the use of other antithrombotic drugs in primary prevention of stroke.

Carotid artery surgery for asymptomatic carotid stenosis

The Asymptomatic Carotid Atherosclerosis Study (ACAS)[438] reports that patients with an asymptomatic carotid stenosis greater than 60% had a 5-year relative risk reduction by 53% of ipsilateral stroke if carotid endarterectomy (CEA) was performed. However, the absolute risk reduction was small (5.9% of strokes in five years), as was the rate of ipsilateral stroke in the medically treated group (11.0% of strokes in five years, or 2.3% annually). These results were assessed with a joint perioperative mortality and morbidity rate of only 2.3%. Furthermore, the five-year results were calculated on the basis of a two-year follow-up and extrapolated, which reduces the reliability of the effect size.

In a recently published study (ACST), 3120 asymptomatic patients with substantial carotid narrowing were randomized equally between immediate carotid endarterectomy (CEA), half of them received CEA within 1 month, and deferred CEA. Patients were followed up for up to 5 years (mean 3.4 years). In asymptomatic patients younger than 75, with carotid diameter reduction of about ³70% on ultrasound immediate CEA halved the net five-year stroke risk from about 12% to about 6% including the 3% perioperative hazard[439].

A meta-analysis of CEA for patients with asymptomatic carotid stenosis with a total of 5223 patients revealed that CEA for asymptomatic carotid stenosis reduced the risk of ipsilateral stroke and any stroke by approximately 30% over three years. However, the absolute risk reduction was small (approximately 1% *per* year over the first few years of follow up in the two largest and most recent trials) but it could be higher with longer follow up[440].

Carotid artery angioplasty and stenting for asymptomatic stenosis

There are no data from randomized trials about the benefits and risks of carotid angioplasty, with or without stenting, compared with endarterectomy in asymptomatic patients[441].

Atrial fibrillation

Atrial fibrillation (AF) is a common cardiac arrhythmia and is an important risk factor for stroke associated with a high rate of ischemic stroke, the risk being similar whether AF is sustained or paroxysmal/intermittent with established effective therapy for stroke prevention[442,443]. The annual risk of stroke in unselected patients with nonvalvular AF is 5%, with a wide variation among subpopulations of AF patients between 0.5% and 12% *per* year. Aggregate analysis of several trials shows that oral anticoagulation therapy with a vitamin K antagonist, warfarin, reduces the rate of ischemic stroke by 70% compared with untreated patients[444]. Assessment of the optimal intensity of anticoagulation therapy producing an INR between 2.0 and 2.9 reduced the combined incidence rate for both ischemic and hemorrhagic events by 80% when compared with an INR below 2.0[445]. When tested with the INR above 5.0, the risk of bleeding became unacceptable, whereas no significant reduction in thromboembolism was seen with INR below 2.0[445].

In four separate randomized trials the effect of ASA was assessed. ASA yielded a pooled risk reduction of 21% compared with placebo. In two of these trials, ASA was significantly less efficacious than warfarin[446].

The Framingham Heart Study noted a dramatic increase in stroke risk associated with AF with advancing age, from 1.5% in those aged 50-59 to 23.5% in those aged 80-89[447]. As the annual rate of stroke among people with AF is very wide, risk stratification should be used to determine whether patients are to be given anticoagulation, aspirin or nothing. Patients with AF and no other cardiovascular disease aged less than 65 are at such a low risk that they should not be treated or should be treated with aspirin, while patients over 60 years without other risk factors may be considered as being at a moderate risk and therapy could include warfarin or aspirin[444]. The dose of aspirin should be 325 mg a day, because this dosage has proved effective in patients with AF[442].

For patients over 75 years of age, a lower target INR of 2.0 (1.6-2.5) may be more sensible to prevent hemorrhage. However, this lower warfarin level has not been established, and many authors disregard age and accept a higher INR target of 2.5.

Also, there are other patients in whom aspirin might be preferred to warfarin: history of previous hemorrhage, over 80 years of age, unstable anticoagulation control because of poor drug or clinical compliance, history of uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg), alcohol abuse and liver disease[448]. In these patients, the risk of hemorrhage may be increased.

Prosthetic heart valves

The risk of embolic stroke is increased in patients with all prosthetic heart valves. It seems that patients with mechanical valves have a higher risk than subjects with tissue valves. Anticoagulation has been proven effective for preventing stroke in patients with prosthetic heart valves. Long-term anticoagulation is recommended for patients with AF who have mitral valve disease or prosthetic heart valves (mechanical or tissue valves). The target INR should be based on the particular type of prosthesis, but not less than 2-3[449].

Recommendations

1. A low salt, low saturated fat diet rich in fish, fruit, vegetable and fiber is recommended (Level II).
2. Regular physical activity is recommended (Level II).
3. Subjects with an elevated body mass index should reduce their weight (Level II).
4. Cigarette smoking should be discouraged (Level II).
5. Heavy use of alcohol should be avoided, while light or moderate alcohol consumption may be protective against stroke (Level I).
6. It is recommended to avoid stress or to learn how to cope with it (Level IV).
7. It is recommended to avoid high estrogen content of OCs, and avoid OCs in all women older than 35 years with other vascular risk factors (Level II).
8. It is recommended to avoid the use of cocaine (Level IV).
9. Hormone replacement therapy should not be used for primary prevention of stroke (Level I).
10. Treatment of hypertension is strongly recommended as the most effective means of decreasing morbidity and mortality due to either ischemic or hemorrhagic stroke (Level I).

10a. Blood pressure should be kept below 140/90 mm Hg (below 130/80 mm Hg in diabetics) by means of lifestyle modifications and/or pharmacological treatments (Level I).

11. Although strict control of glucose levels in DM has not yet been proven to be associated with a decreased risk of stroke in general, it should be encouraged because of the benefits in terms of other diabetic complications (Level III).
12. Cholesterol-lowering therapy with statins is recommended for high-risk patients (Level I).
13. There is no scientific support for prescribing ASA to reduce the risk of stroke in asymptomatic patients. However, ASA will reduce the risk of MI and can be recommended in population with one or more vascular risk factors (Level I).
14. Other antithrombotic drugs (clopidogrel, ticlopidine and dipyridamole) have not been studied in asymptomatic subjects and therefore cannot be recommended for primary stroke prevention (Level IV).
15. CEA should be performed immediately (within a month) in asymptomatic patients with a 60%-99% stenosis of the internal carotid artery, with life expectancy of at least 5 years, and in centers with joint perioperative complication rate, stroke and death of <3% (Level I).
16. Carotid angioplasty, with or without stenting, is not recommended for patients with asymptomatic carotid stenosis.
17. All patients with AF aged 60-75 years at a high risk of stroke should be considered for long-term oral anticoagulation therapy (target INR 2.5; range 2.0-3.0) (Level I).

17a. Patients unable to receive oral anticoagulation therapy should be offered ASA (Level I).

18. Patients with non-valvular AF aged less than 60 years with no additional vascular risk factors should be considered for ASA 325 mg *per* day or no therapy (Level I).
19. Patients over 65 years of age without vascular risk factors could be prescribed either anticoagulants or aspirin 325 mg *per* day (Level III).
20. In patients over 75 years of age, warfarin may be used as an option, with a lower INR (target INR of 2.0; range 1.6-2.5) to decrease the risk of hemorrhage (Level III).
21. Patients 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 (Level II).

SECONDARY PREVENTION

Secondary prevention means treatment and rehabilitation of patients who have had a stroke or transient ischemic attack in order to prevent recurrent stroke. Secondary prevention can extend overall survival, improve the quality of life, decrease the need of surgical procedures, and reduce the incidence of subsequent strokes. Secondary prevention comprises changing of lifestyle: quitting smoking, increasing physical activity, reducing body weight, changing eating habits, etc., treatment of concomitant diseases: hypertension, diabetes, elevated plasma lipids, cardiac diseases, atrial fibrillation etc., and prescribing drugs for secondary prevention of ischemic stroke and surgical interventions: carotid endarterectomy and angioplasty. Lifestyle modifications, treatment of concomitant diseases and surgical interventions are measures of secondary prevention for ischemic as well as for hemorrhagic stroke, while prescribing antiplatelet and anticoagulant drugs are only reserved for secondary prevention of ischemic stroke[299]. Everything that has been said in primary prevention regarding diet, physical activity, obesity, cigarette smoking, alcohol consumption and stress should also be used in secondary stroke prevention.

Antiplatelet drugs

Four antiplatelet agents have been shown to reduce the risk of ischemic stroke after a stroke or TIA: acetylsalicylic acid, ticlopidine, clopidogrel and dipyridamole[450, 451]. In a meta-analysis of results of 21 randomized trials comparing antiplatelet therapy with placebo in 18,270 patients with prior stroke or TIA, antiplatelet therapy was associated with a 28% relative odds reduction in nonfatal strokes and a 16% reduction in fatal strokes[452].

Acetylsalicylic acid

Acetylsalicylic acid (ASA) is an irreversible inhibitor of cyclooxygenase. ASA has been in use for more than 100 years and it is the best studied medical therapy for preventing stroke. The Antiplatelet Trialists' Collaboration performed a meta-analysis of 145 trials involving 51,144 patients allocated to antiplatelet therapy[272]. They found a 25% (20%-28%) reduction in stroke risk among patients receiving ASA. The latest publication from the Antithrombotic Trialists Collaboration[452] involved the meta-analysis of 287 trials with 135,000 patients in comparison with antiplatelet therapy *versus* controls and 77,000 in comparison with different antiplatelet regimens, finding similar results for ASA.

It has been debated that low doses could be more effective than medium or high doses because the production of prostacycline by the endothelial cells may be partially preserved[453]. Trials comparing different doses of aspirin in TIA or stroke patients (1200 *vs.* 300 mg/day and 283 *vs.* 30 mg/day)[454,455] showed that high- and low-dose aspirin had similar efficacy in preventing vascular events. It seems that ASA in any daily dose =30 mg/day leads to a moderate but significant reduction of stroke. A major side effect of ASA is bleeding. Higher doses of aspirin have been associated with a greater risk of gastrointestinal hemorrhage[452]. The recommended dose of ASA therefore should be between 75 and 150 mg[456].

Ticlopidine

Ticlopidine is a thienopyridine derivative that inhibits the adenosine diphosphate pathway of platelet aggregation. In the Canadian American Ticlopidine Study (CATS), ticlopidine 2x250 mg/day showed a 23% relative reduction in the risk of composite outcome[457]. In the Ticlopidine Aspirin Stroke Study (TASS), ticlopidine 2x250 mg/day was associated with a 21% RR reduction in stroke during a 3-year follow-up and produced a more modest and nonsignificant 9% reduction in the risk of the combined outcome of stroke, MI, or vascular death[458]. In the African American Aspirin Stroke Prevention Study (AAASPS), ticlopidine 2x250 mg/day showed no difference in the risk of the combination of stroke, MI, or vascular death at 2 years compared to ASA 650 mg/day[459].

Major disadvantages of ticlopidine are gastrointestinal side effects: diarrhea, dyspepsia and bleeding, skin rashes, and more serious bone marrow side effects: neutropenia, thrombocytopenia, and thrombotic thrombocytopenic purpura. Most of these side effects occur in the first three months, but thrombotic thrombocytopenic purpura can occur even after the first three months[460,461]. Ticlopidine is a drug with more side effects than ASA.

Clopidogrel

Clopidogrel is a new thienopyridine derivative, chemically related to ticlopidine. It inhibits platelet aggregation by inhibiting the adenosine diphosphate P2Y12 receptor. The Clopidogrel *versus* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study com-

pared the effects of 75 mg clopidogrel and 325 mg ASA once daily in reducing the composite endpoint of ischemic stroke, MI, or vascular death in 19,185 patients and found a significant 8.7% relative reduction in events in favor of clopidogrel[462]. In a subgroup analysis of those patients with prior stroke, the risk reduction with clopidogrel was slightly smaller and nonsignificant. Two post-hoc analyses indicated that diabetics and those with pre-existing ischemic stroke or MI received relatively more benefit from clopidogrel than from ASA[463,464]. The side effects of clopidogrel and ASA were similar. Neutropenia is not a problem with clopidogrel, but cases of thrombotic thrombocytopenic purpura associated with clopidogrel use have been described[465]. Copidogrel should be used in patients with contraindications to, or adverse effects on ASA.

Dipyridamole*

Dipyridamole is an antiplatelet agent with inhibition of cyclic nucleotide phosphodiesterase and blockage of the uptake of adenosine[466]. The Antithrombotic Trialists analyzed all trials involving dipyridamole alone *versus* placebo. They found fifteen trials comparing dipyridamole alone *vs*. placebo and showed a 16% odds reduction for stroke, MI, or vascular death favoring dipyridamole[452]. None of these trials used extended-release dipyridamole. Headache is the most common side effect of extended-release dipyridamole. Bleeding was not significantly increased with dipyridamole. A post hoc analysis from ESPS-2 that used extended-release dipyridamole showed no excess of adverse cardiac events as compared with placebo or ASA[467].

Combined antiplatelet therapy Dipirydamole* and ASA

The Antithrombotic Trialists found forty-six trials that compared dipyridamole combined with ASA *vs.* placebo and showed a 30% odds reduction in stroke, MI, or vascular death favoring the combination[452]. However, in the 1980s, this combination was evaluated only in several trials that included patients with cerebral ischemia. Some trials found that the combination of dipyridamole plus ASA was superior to ASA alone, and some of them did not[468-470].

In the late 1980s, the European Stroke Prevention Study (ESPS-1) showed that combination therapy (225 mg/day dipyridamole plus 975 mg/day ASA) reduced the risk of combined stroke and death by 33% and the risk of stroke alone by 38% compared with placebo[471]. The European Stroke Prevention Study II analyzed 6602 patients with stroke or TIA who were randomized to ASA alone (50 mg/day), extended-release dipyridamole alone (400 mg/day), ASA plus extended-release dipyridamole (50 + 400 mg/day), or placebo. The risk of stroke was significantly reduced, by 18% on ASA alone, 16% with dipyridamole alone, and 37% with a combination of ASA plus dipyridamole. The combination was superior to ASA in reducing stroke recurrence by 23%, and 25% superior to dipyridamole alone[472].

In the recently published ESPRIT study, 2763 patients were assigned to ASA (30-325 mg/day, median ASA dose was 75 mg) with (n=1363) or without (n=1376) dipyridamole (2x200 mg/day) within 6 months after a TIA or minor stroke. After a mean follow-up of 3.5 years, primary outcome events (composite of death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication) arose in 173 (13%) patients on ASA and dipyridamole and in 216 (16%) on ASA alone (hazard ratio 0.80, 95% CI 0.66-0.98; absolute risk reduction 1.0% *per* year, 95% CI 0.1-1.8). Ischemic stroke occurred in 96 patients on ASA and dipyridamole and in 116 patients on ASA alone (hazard ratio 0.84, 95% CI 0.64-1.10). Major bleeding complications occurred in 35 patients on ASA and dipyridamole and in 53 patients on ASA alone (hazard ratio 0.67, 95% CI 0.44-1.03). The addition of the ESPRIT data to the meta-analysis of previous trials resulted in an overall risk ratio for the composite of vascular death, stroke, or myocardial infarction of 0.82 (95% CI 0.74-0.91)[473].

Clopidogrel and ASA

The MATCH trial included 7599 patients with a prior stroke or TIA plus additional risk factors who were allocated to clopidogrel 75 mg/day or combination therapy with clopidogrel 75 mg/day plus ASA 75 mg/day. The primary outcome was the composite of ischemic stroke, MI, vascular death, or rehospitalization secondary to ischemic events. There was no significant benefit of combination therapy compared with clopidogrel alone in reducing the primary outcome or any of the secondary outcomes. However, the risk of major hemorrhage was significantly increased in the combination group compared with clopidogrel alone, with a 1.3% absolute increase in life-threatening bleeding. Although clopidogrel plus ASA is recommended over ASA for acute coro-

nary syndromes, with most guidelines advocating up to 12 months of treatment, the results of MATCH do not suggest a similar risk-benefit ratio for secondary stroke prevention[474]. Also, in the recently published ACTIVE W study, the risk of bleeding was higher with a combination of clopidogrel and ASA a compared with oral anticoagulant (vitamin K antagonist)[475].

In the recently published CHARISMA trial, 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors were assigned to receive clopidogrel (75 mg/day) plus low-dose ASA (75 to 162 mg/day) or placebo plus low-dose ASA. After a follow-up of 28 months, the rate of the primary efficacy end point (composite of myocardial infarction, stroke, or death from cardiovascular causes) was 6.8% with clopidogrel plus ASA and 7.3% with placebo plus ASA (relative risk - RR, 0.93; 95% CI 0.83-1.05; p=0.22). The rate of the primary end point among patients with multiple risk factors was 6.6% with clopidogrel and 5.5% with placebo (RR 1.2; 95% CI 0.91-1.59; p=0.20), and the rate of death from cardiovascular causes was also higher with clopidogrel (3.9% *vs.* 2.2%, p=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel and 7.9% with placebo (RR 0.88; 95% CI 0.77-0.998; p=0.046). Nonfatal ischemic stroke occurred in 1.7% of patients in the clopidogrel group and in 2.1% of patients in the placebo group (RR 0.81, 95% CI 0.64-1.02, p=0.07). Nonfatal stroke occurred in 1.9% of patients in the clopidogrel group and 2.4% of patients in the placebo group (RR 0.79, 95% CI 0.64-0.98, p=0.03). The rate of moderate bleeding was 2.1% in the clopidogrel group, as compared with 1.3% in the placebo group (RR 1.62; 95% CI 1.27 to 2.08; p<0.001). The rate of intracranial hemorrhage was similar in both treatment groups. Overall, clopidogrel plus ASA was not significantly more effective than ASA alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes[476].

Selection of antiplatelet therapy

Many factors may guide the selection of specific antiplatelet drug after TIA or ischemic stroke such as comorbid illnesses, side effects, and costs. ASA is the least expensive drug, which can be important in long-term therapy. However, even small reductions in vascular events compared with ASA may make the combination of ASA and extended-release dipyridamole cost-effective from a broader social perspective. For patients intolerant to aspirin because of allergy or gastrointestinal side effects, clopidogrel is an appropriate choice. Dipyridamole may be poorly tolerated by some patients because of persistent headache. At present, the selection of antiplatelet therapy after stroke and TIA should be individualized[450, 451].

Recommendations

1. For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents are recommended to reduce the risk of recurrent stroke and other cardiovascular events (Level I).
2. ASA (50 to 325 mg/day) should be given to reduce stroke recurrence (Level I).
3. Where available, the combination of ASA and extended-release dipyridamole* , and clopidogrel are acceptable options for initial therapy (Level I).
4. The combination of ASA and extended-release dipyridamole is more effective than ASA alone and dipyridamole alone (Level I).
5. Patients starting treatment with thienopyridine derivatives should receive clopidogrel instead of ticlopidine because it has fewer side effects (Level I).
6. The addition of ASA to clopidogrel increases the risk of hemorrhage and is **not** recommended for ischemic stroke or TIA patients (Level I)
7. Patients who do not tolerate ASA or thienopyridine derivatives may be treated with extended-release dipyridamole* (2x200 mg/day) (Level I).

Oral anticoagulants for atrial fibrillation

Multiple clinical trials have demonstrated the superior therapeutic effect of oral anticaogulation (most often using warfarin) as compared with placebo in reducing the risk of recurrent stroke in patients with atrial fibrillation and recent ischemic stroke. The optimal intensity of oral anticoagulation for stroke prevention in patients with AF appears to be INR 2.0-3.0. Results from trials suggest that the efficacy of oral anticoagulation declines significantly below an INR of 2.0[477-479].

Evidence supporting the efficacy of ASA is substantially weaker than that for warfarin. A pooled analysis of data trials resulted in an estimated RR reduction of 21% compared with placebo (95% CI, 0-38)[446].

* Drug not registered in Croatia

In the recently published Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) patients having AF plus one or more risk factors for stroke were randomly allocated to oral anticoagulation therapy with vitamin K antagonist (target INR 2.0-3.0; n=3371) or clopidogrel (75 mg/day) plus ASA (75-100 mg/day recommended; n=3335). There were 165 primary events in patients on oral anticoagulation therapy (annual risk 3.93%) and 234 in those on clopidogrel plus ASA (annual risk 5.60%; RR 1.44 (95% CI 1.18-1.76; p=0.0003). The study was stopped early because of clear evidence for oral anticoagulation therapy to be superior to clopidogrel plus ASA in the prevention of vascular events in patients with AF at a high risk of stroke. The rates of major hemorrhage were similar in the two groups, but significantly more minor bleeds occurred with clopidogrel plus ASA than with oral anticoagulation therapy. Total bleeds were also significantly more likely with clopidogrel plus ASA than with oral anticoagulation therapy[475].

Ximelagatran is a direct thrombin inhibitor that is orally administered, does not need anticoagulation monitoring or dose adjustment, has stable pharmacokinetics independent of the hepatic P450 enzyme system, has a low potential for food or drug interactions, and it was developed to be an easier drug to administer than adjusted-dose warfarin. The Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Atrial Fibrillation (SPORTIF) -III and -V compared ximelagatran with dose-adjusted warfarin (INR 2-3) in high-risk patients with AF. Ximelagatran was administered at a fixed dose of 2x36 mg/day without coagulation monitoring. SPORTIF-III was an open-label study, and SPORTIF-V was a double-blind trial. About 25% of patients in these trials had a history of stroke or TIA. In both trials, ximelagatran was not inferior to warfarin and was associated with fewer bleeding complications. The primary outcome event rate in patients with prior stroke was 2.83% *per* year in the ximelagatran group and 3.27% *per* year in the warfarin group (p=0.63). There were no significant differences between treatments in rates of hemorrhagic stroke, fatal bleeding, or other major bleeding, but combined rates of minor and major bleeding were significantly lower with ximelagatran (31.7% *vs.* 38.7% *per* year; p<0.0001). The results of SPORTIF-III and -V provide evidence that ximelagatran 2x36 mg/day is essentially equivalent to well-controlled, dose-adjusted warfarin at INRs of 2.0-3.0[480]. Since the FDA and European regulatory authorities have not yet approved ximelagatran, it is not included in recommendations.

Although evidence from randomized trials is still lacking, long-term anticoagulants are routinely used in patients with mechanical prosthetic valves. In this setting a higher target of an INR between 2.5 and 3.5 is recommended[481]. In patients with valvular heart disease, MI and left ventricular thrombus, heart failure, cardiomyopathy, arrhythmia other than AF, patent foramen ovale, long-term anticoagulation with an INR of 2.0-3.0, or antiplatelet therapy (ASA 325 mg/day) may be indicated.

Recommendations

1. Oral anticoagulation with a target INR between 2.0 and 3.0 is indicated after ischemic stroke associated with persistent or paroxysmal (intermittent) atrial fibrillation (Level I)
2. For patients unable to take oral anticoagulants, ASA 325 mg/day is recommended (Level I)
3. Patients with mechanical prosthetic valves should receive long-term anticoagulation therapy with a target INR between 2.5 and 3.5 (Level III)
4. Patients with confirmed cardioembolic stroke should receive anticoagulation if the risk of recurrence is high, with a target INR between 2.0 and 3.0 (Level III)

Antihypertensive therapy

In comparison with abundant evidence from a variety of sources that support the importance of treatment of hypertension for primary cardiovascular disease prevention in general and in stroke in particular, data on the role of blood pressure treatment for secondary prevention in persons with stroke or TIA are relatively scarce[482,483]. No relevant trials tested the effects of non-pharmacological interventions. A continuous association has been demonstrated between both systolic and diastolic blood pressure and the risk of recurrent ischemic stroke[484]. Treatment with antihypertensive drugs has been associated with significant reductions in all recurrent strokes, nonfatal recurrent stroke, MI, and all vascular events with similar but nonsignificant trends towards reduction in fatal stroke and vascular death.

A meta-analysis from 9 randomized controlled trials on antihypertensive drugs, in which a small number of stroke survivors had been included, led to an estimated RRR of 29% (95% CI 5-47)[484]. A systematic review fo-

cused on the relationship between blood pressure reduction and secondary prevention of stroke and other vascular events. The analysis including 7 published, nonconfounded, randomized controlled trials with a combined sample size of 15,527 subjects with ischemic stroke, TIA, or ICH showed that blood pressure lowering or treating hypertension with a variety of antihypertensive agents reduced stroke (odds ratio 0.76; 95% CI, 0.63 to 0.92)[486]. The PATS trial assessed indapamide (2.5 mg daily, a thiazide-like diuretic) in a double-blind placebo-controlled trial involving 5,665 Chinese patients with high blood pressure and recent stroke or TIA: indapamide lowered blood pressure by 5/2 mm Hg and reduced the risk of recurrent stroke by 29% (ARR 2.9% over 3 years)[487].

Data on the relative benefits of specific antihypertensive regimens for secondary stroke prevention are largely lacking. A meta-analysis including patients with ischemic stroke, TIA, or hemorrhagic stroke showed a significant reduction in recurrent stroke with diuretics and diuretics combined with ACEIs, but not with beta-blockers or ACEIs used alone. The overall reductions in stroke and all vascular events were related to the degree of blood pressure lowering achieved[484].

However, the HOPE study showed an effective prevention of secondary ischemic events by an ACE inhibitor (ramipril) in stroke patients[418]. The occurrence of the primary outcome (MI, stroke, death from cardiovascular causes) was significantly reduced in the ramipril group as compared with the placebo group (RRR 0.78; 95% CI: 0.70-0.80). This result was observed despite a modest blood pressure reduction in the ramipril group and was also present in the subgroup of patients who had already had a stroke at inclusion[485]. These results could indicate that ACEI might have some additional benefits besides blood pressure lowering.

The Perindopril Protection against Recurrent Stroke Study (PROGRESS) was a double-blind, randomized trial comparing the ACEI perindopril (4 mg/day) with or without diuretic indapamide (2-2.5 mg/day) *versus* placebo for the prevention of recurrent ischemic stroke in individuals with a history of non-disabling cerebrovascular disease (minor stroke or TIA) irrespective of blood pressure. Antihypertensive treatment was initialized at least 2 weeks after stroke. The PROGRESS study included 6,105 patients and showed that blood pressure lowering by an average of 9/4 mm Hg with perindopril-based therapy decreased the risk of recurrent stroke by 28% *versus* placebo. Patients receiving perindopril and indapamide had a mean drop in blood pressure of 12/5 mm Hg and a 43% reduction in the risk of stroke. Interestingly, the observed benefit was achieved regardless of blood pressure at entry and type of stroke. These beneficial effects were present in all stroke subtypes, but were greater in hemorrhagic strokes (RRR 50%; 95% CI: 33-74) and in Asians. The combination therapy prevented 1 recurrent stroke for 14 patients treated during a 5-year period. However, there was no significant benefit when perindopril was given alone[489].

A preliminary phase II study randomized 342 hypertensive patients with acute ischemic stroke to an angiotensin receptor blocker (ARB) or placebo over the first week. There were no significant differences in blood pressures between the active treatment and placebo patients, with both groups receiving the ARB after the first week. Although the number of vascular events in the ARB group was significantly reduced over the first week (OR, 0.475; 95% CI, 0.252 to 0.895), at 12 months a significant reduction in mortality was observed in the ARB group[490].

Recommendations

1. Antihypertensive treatment is recommended for prevention of recurrent stroke and in persons who have had an ischemic stroke or TIA (Level I). Because this benefit extends to persons with and without a history of hypertension, this recommendation should be considered for all ischemic stroke and TIA patients (Level II).
2. The optimal drug regimen remains uncertain. Although all major classes of antihypertensives are suitable for blood pressure control, most patients will require >1 agent. However, the available data support the use of diuretics and a combination of diuretics and ACEI or ARB (Level II). However, the choice of specific drugs and targets should be individualized on the basis of reviewed data and consideration of specific patient characteristics.
3. ACEIs and ARBs are more effective in reducing the progression of renal disease; ACEI (ramipril) is recommended as first-choice medication for patients with diabetes (Level I).
4. An absolute target blood pressure level and reduction are not certain and should be individualized, but benefit has been associated with an average reduction of approximately 10/5 mm Hg. However, blood pressure should probably be kept below 140/90 mm Hg and below 130/80 mm Hg in diabetics (Level II).

Cholesterol-lowering therapy

An overview of randomized clinical trials published in 2000 showed that lowering cholesterol was associated with a reduction in mortality and fatal CHD, but a non-significantly increased risk of fatal stroke[491]. The PROSPER trial showed reduction in the risk of coronary events under pravastatin in older individuals, without a significant effect on stroke and cognition during a mean follow-up of 3 years[428]. However, the MIRACL substudy found that atorvastatin reduced total stroke by 51%: fatal or nonfatal stroke occurred in 12 atorvastatin patients and 24 placebo patients (RR 0.49; 95% CI 0.24 to 0.98; p=0.04) among patients with acute coronary syndromes[491].

The MRC/BHF Heart Protection Study had a subgroup of 1,820 patients with previous stroke or TIA and without CHD. Simvastatin (40 mg daily) reduced the risk of recurrent vascular events in this subgroup by 24%. The RR of any stroke was lowered by 25% across the whole trial involving patients with vascular disease and did not increase the risk of hemorrhagic stroke[429]. In the meta-analysis of all randomized trials testing statin drugs published before August 2003, the relative risk reduction for stroke was 21% (odds ratio (OR) 0.79 (0.73-0.85)). Fatal strokes were reduced but not significantly by 9% (OR, 0.91 (0.76-1.10)). There was no increase in hemorrhagic strokes (OR, 0.90 (0.65-1.22)). Statin size effect was closely associated with LDL-cholesterol reduction. Each 10% reduction in LDL-cholesterol was estimated to reduce the risk of all strokes by 15.6% (95% CI, 6.7 to 23.6)[493].

In the recently published SPARCL study, 4731 patients who had a stroke or TIA within 1-6 months before study entry were allocated to atorvastatin 80 mg/day or placebo. During a median follow-up of 4.9 years, 265 (11.2%) patients in the atorvastatin group and 311 (13.1%) patients in the placebo group had a fatal or nonfatal stroke (adjusted hazard ratio, 0.84; 95% CI, 0.71 to 0.99; p=0.03), while the 5-year absolute risk reduction was 2.2%. The atorvastatin group had 218 ischemic strokes and 55 hemorrhagic strokes, whereas the placebo group had 274 ischemic strokes and 33 hemorrhagic strokes. The overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group (p=0.98), as were the rates of serious adverse events[494].

The beneficial effect of statins in reducing stroke in patients with vascular disease appears to be independent of other risk factors (age, gender, cholesterol level) and prophylactic measures[424,429]. The risk reductions with statins seem to be beyond that expected solely through cholesterol reductions and have led to the consideration of other potential beneficial mechanisms[495,496].

There is also some evidence that other medications used to treat dyslipidemia can be used in stroke or TIA patients who cannot tolerate statins. Niacin was associated with a reduction in cerebrovascular events in the Coronary Drug Project[497]. Gemfibrozil reduced the rate of total strokes among men with coronary artery disease and low levels of HDL-cholesterol in the Veterans Administration HDL Intervention Trial[498].

Recommendations

1. Patients with ischemic stroke or TIA should receive statins (Level I).
2. The target cholesterol level is =5 mmol/L and LDL-cholesterol is =3 mmol/L (Level I).
3. More rigorous control of cholesterol should be considered in patients with diabetes (Level II).
4. Patients with ischemic stroke or TIA that do not tolerate statins may be considered for treatment with niacin or gemfibrozil (Level II).

Postmenopausal hormone replacement therapy

Despite prior suggestions from observational studies that postmenopausal hormone therapy may be beneficial for the prevention of heart disease and stroke, randomized trials of heart disease and stroke survivors as well as primary prevention trials have failed to demonstrate any significant benefits[499]. The Women's Estrogen for Stroke Trial was a placebo-controlled randomized trial of estrogen replacement therapy for the secondary prevention of ischemic stroke that failed to show any reduction in the risk of stroke recurrence or death with estradiol. During a mean follow-up of 2.8 years, the RR of combined stroke and death in the estrogen group was 1.1 (95% CI 0.8-1.4); estrogen did not reduce the risk of death alone (RR: 1.2; 95% CI: 0.8-1.8) or of nonfatal stroke (RR: 1.0. 95% CI: 0.7-1.4). The risk of fatal stroke was higher in the estrogen group (RR: 2.9: 95% CI: 0.9-9.0) and nonfatal strokes were associated with slightly worse functional deficit[500]. The Heart and Estrogen/Progesterone Replacement Study (HERS) did not demonstrate any benefit of hormone therapy among postmenopausal women who had MI[404,501]. The Women's Health Initiative (WHI), which examined the

role of hormonal therapy for the primary prevention of cardiovascular disease and stroke among postmenopausal women, was stopped early because of an increase in vascular events[502]. Moreover, an increased stroke risk among women with previous hysterectomy who were randomized to hormonal therapy was observed[503].

Recommendation

1. For women with ischemic stroke or TIA, postmenopausal hormone therapy is **not** recommended (Level I).

Carotid artery endarterectomy

For patients with symptomatic atherosclerotic carotid stenosis >70%, as defined using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, the value of carotid endarterectomy (CEA) has been clearly established from the results of 3 major prospective randomized trials: the NASCET, the European Carotid Surgery Trial (ECST), and the Veterans Affairs Cooperative Study Program[504-506]. Among symptomatic patients with TIAs or minor strokes and high-grade carotid stenosis, each trial showed impressive relative and absolute risk reductions for those randomized to surgery.

In the NASCET, patients who underwent carotid endarterectomy had an absolute reduction of 17% in the risk of ipsilateral stroke at 2 years (relative RR 65%). The study showed that the number needed to treat was 6 patients to prevent 1 stroke. However, these results were achieved with a perioperative morbidity and mortality of 5.5% (all strokes and deaths). Restricting the analysis to major stroke and death resulted in a rate of 2.1%. However, these rates did not include the risk of complication of angiography of about 1%. The authors therefore state that the benefit of surgical procedure diminishes when perioperative complications exceed 2.1%, and that it vanishes entirely when the rate approaches 10%. Although the rate of perioperative complications in the ECST was higher (7.5% of deaths, disabling stroke, or any stroke producing symptoms for more than 7 days), surgery-allocated patients still had a significant absolute risk reduction of 6.5% in ipsilateral stroke and a relative risk reduction of 39%.

For patients with symptomatic carotid stenosis in the moderate category (50% to 69% stenosis), there is some uncertainty. The results from NASCET and ECST demonstrated less impressive benefits of CEA in this moderate group as compared with medical therapy[191,192]. In NASCET, the 5-year risk of fatal or nonfatal ipsilateral stroke over the 5-year period was 22.2% in the medically treated group and 15.7% (p=0.045), absolute RR was 6.5% and relative RR 29% in patients treated surgically[507].

For patients with carotid stenosis <50%, these trials showed that there was no significant benefit of surgery. In ECST, no benefit of surgery was demonstrated among those with <50% ipsilateral carotid stenosis. In patients with <50% stenosis in NASCET, there was no significant reduction in the ipsilateral stroke risk among those treated with endarterectomy compared with those treated medically[508].

A meta-analysis of pooled data from the ECST, NASCET and Veterans Affairs Trial[309] showed that carotid surgery increased the 5-year risk of ipsilateral ischemic stroke in patients with less than 30% stenosis (n=1746, absolute risk reduction -2.2%, p=0.05), had no effect in patients with 30%-49% stenosis (1429, 3.2%, p=0.6), was of marginal benefit in those with 50%-69% stenosis (1549, 4.6%, p=0.04), and was highly beneficial in those with 70% stenosis or greater without near-occlusion (1095, 16.0%, p<0.001). There was a trend towards benefit from surgery in patients with near-occlusion at 2-year follow-up (5.6%, p=0.19) [262], but no benefit at 5 years (-1.7%, p=0.9)[509].

In these trials, stenosis was evaluated by angiography. However, it seems that it may be reasonable to proceed with carotid surgery if one or more of the following investigations show a severe stenosis: ultrasonography, magnetic resonance angiography and/or CT angiography.

Carotid artery angioplasty and stenting

Carotid percutaneous transluminal angioplasty is a potentially valuable technique. Its advantages over carotid endarterectomy are short hospital stay, avoidance of general anesthesia and surgical incision, and the ability to treat surgically inaccessible sites, such as the internal carotid artery stenosis at the base of the skull. Moreover, carotid percutaneous transluminal angioplasty and stenting (CAS) may be the most effective means of treating restenosis after initial carotid endarterectomy[510].

The Wallstent Trial randomized 219 symptomatic patients with 60% to 90% stenosis to CEA or CAS. CAS was performed without distal protection and currently accepted antiplatelet prophylaxis. Study design allowed operators with limited experience to participate. The

risk of perioperative stroke or death was 4.5% for CEA and 12.1% for CAS, and the risk of major stroke or death at 1 year was 0.9% for CEA and 3.7% for CAS. The trial was halted because of poor results from CAS[511].

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) randomly compared angioplasty with surgical therapy in 504 symptomatic carotid patients, of whom only 26% received stents. Major outcome events within 30 days did not differ between endovascular treatment and surgery groups, with a 30-day risk of stroke or death of 10.0% and 9.9%, respectively, i.e. both groups carried a higher risk than in NASCET, ECST or ACAS. Despite the increased risk of severe ipsilateral carotid stenosis in the endovascular group at 1 year, no substantial difference in the rate of ipsilateral stroke was noted up to 3 years after randomization[512].

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized 334 patients (30% symptomatic) to endarterectomy or stenting with the use of an emboliprotection device, testing the hypothesis that stenting was not inferior to endarterectomy. CAS operators had a periprocedural stroke, death or MI complication rate of 4%. The primary end-point of the study (the cumulative incidence of death, stroke, or MI within 30 days after the intervention, or death or ipsilateral stroke between 31 days and 1 year) occurred in 20 stent patients and 32 endarterectomy patients (30-day risk, 5.8% *vs.* 12.6%; p=0.004 for noninferiority). Most of the benefit was detected in the lower risk of MI for the stent compared with the high-surgical risk endarterectomy cases[513]. Several randomized trials comparing CEA and CAS are ongoing.

CAS has been used in selected patients with carotid stenosis that is difficult to access surgically, medical conditions that increase the risk of surgery, or other specific circumstances such as radiation-induced carotid stenosis or restenosis after CEA. More evidence is needed for definite evaluation of angioplasty plus stent for patients with extracranial carotid stenosis.

Recommendations

1. For patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, carotid endarterectomy is indicated, but only in centers with a perioperative complication rate (all strokes and death) less than 6% (Level I).
2. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis without a severe neurological deficit, carotid endarterectomy may be recommended, depending on the patient-specific factors such as age, gender and comorbidities. This is also valid only for centers with a perioperative complication rate (all strokes and death) less than 6%. The subgroup of patients most likely to benefit from surgery are males with recent hemispheric symptoms (Level III).
3. Carotid endarterectomy is not recommended in patients with stenosis less than 50% (Level I).
4. Carotid endarterectomy should not be performed in centers that do not exhibit low complication rates equal to those in NASCET and ECST (Level I).
5. When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is suggested rather than delaying surgery (Level II).
6. Patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk of surgery, radiation-induced stenosis is present, or in case of restenosis after carotid endarterectomy, carotid artery stenting is not inferior to endarterectomy and may be considered. Carotid artery stenting is reasonable when performed by operators with established periprocedural morbidity and mortality rates of less than 6% (Level III).

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Sažetak

Ovaj članak predstavlja osuvremenjene Preporuke za zbrinjavanje moždanog udara koje su prvi puta objavljene u ovom časopisu 2001. godine. Preporuke su u skladu s preporukama triju europskih društava koja su zastupljena u Europskoj inicijativi za moždani udar (European Stroke Initiative – EUSI): Europsko vijeće za moždani udar, Europsko neurološko društvo, Europsko udruženje neuroloških društava, i u skladu su s Preporukama Američkog udruženja za srce/Američkog društva za moždani udar, a odobrila ih je Američka akademija neurologa. Ove Preporuke su prihvaćene od Hrvatskoga društva za neurovaskularne poremećaje Hrvatskoga liječničkog zbora, Hrvatskoga društva za moždani udar i Klinike za neurologiju Kliničke bolnice "Sestre milosrdnice" koja je Referentni centar Ministarstva zdravstva Republike Hrvatske.

Ključne riječi: *Moždani udar; Cerbrovaskularne bolesti; Terapija moždanog udara; Smjernice; Trombolitična terapija; Jedinice za liječenje moždanog udara*