Atherosclerosis: The 21st Century Epidemic
Pontifical Academy of Sciences, Scripta Varia 116, Vatican City 2011
www.pas.va/content/dam/accademia/pdf/sv116/sv116-hacke.pdf

Acute Stroke Treatment: A Window of Opportunity[1]

Werner Hacke

Introduction

Stroke is a medical and occasionally also a surgical emergency. Stroke rates are on the rise all over the world and stroke has become the number one cause of mortality in several parts of the world including China, Russia and India. We may expect a doubling of strokes in the next 3 decades with the increase of life expectancy.

The success of care of the acute stroke victim begins with the recognition both by the public and the health professionals [Wang, 2001] that stroke is an emergency, like acute myocardial infarction or trauma. Care of the acute stroke victim as an emergency depends on a four-step chain:

1. Rapid recognition and reaction to stroke warning signs,
2. Immediate EMS contact and priority EMS dispatch,
3. Priority transport with notification of the receiving hospital,
4. Immediate emergency room triage, clinical, laboratory and imaging evaluation, accurate diagnosis, therapeutic decision and administration of appropriate treatments at the receiving hospital.

Referral

Applying the 'time is brain' concept means that medical attention and treatment of stroke should be considered as an emergency. Thus, avoiding time delays should be the major aim in the prehospital phase of acute stroke care. This has far-reaching implications for recognition of signs and symptoms of stroke by the patient himself or his relatives or bystanders, the means of first medical contact, and transportation to hospital. In several studies, delays have been identified at three different levels of acute stroke management [Kwan, 2004]:

1. Delays at the population level attributed to a failure to recognise the symptoms of stroke and contact emergency services.

[1] This manuscript is based on the ESO-Guidelines for ischemic stroke management. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008 - Hacke W for The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. *Cerebrovascular Diseases* 25, 5:457-507.

2. Delays at the level of the emergency services and emergency physicians due to failure to prioritise stroke transport.
3. Delays at the hospital level due to delays in neuroimaging and inefficient in-hospital acute stroke care.

A large amount of time is lost outside the hospital [Evenson, 2001]; for stroke patients of a Portuguese university hospital this accounted for 82% of time [Ferro, 1994]. Studies that identify demographic, social, cultural, behavioural and clinical factors associated with longer prehospital time may provide targets for educational campaigns [Moser, 2006; Gil Nunez, 2004]

To improve the accuracy of stroke identification and speed up transfer to the hospital education should also be directed to paramedics and ED staff [Kwan, 2004]. Education of paramedics increased stroke knowledge, clinical and communication skills [Gordon, 2005 #336] and decreased prehospital delay [Behrens, 2002 #298].

Recommendations

- *Immediate emergency medical system (EMS) contact and priority EMS dispatch are recommended (Class II, Level B).*
- *Priority transport with advance notification of the receiving hospital (outside and inside hospital) is recommended (Class III, Level B).*
- *Suspected stroke victims should be transported without delay to the nearest medical centre with a stroke unit that can provide ultra-early treatment (Class III, Level B).*
- *Dispatchers and ambulance personnel should be trained to recognise stroke using simple instruments such as the Face Arm Speech Test (Class IV, Level GCP).*
- *Immediate emergency room triage, clinical, laboratory and imaging evaluation, accurate diagnosis, therapeutic decision and administration of appropriate treatments at the receiving hospital is recommended (Class III, Level B).*
- *In remote or rural areas helicopter transfer should be considered to improve access to treatment (Class III, Level C).*
- *In remote or rural areas telemedicine should be considered to improve access to treatment (Class II, Level B).*

In-hospital treatment

In-hospital delay may account for 16% of total time lost from stroke onset to CT [Ferro, 1994]: Reasons for in-hospital delays are a lack of identifying stroke as emergency, inefficient in-hospital transport, delayed medical assessment, delay in imaging or an uncertainty in administering rt-PA [Kwan, 2004; Evenson, 2001; Gil Nunez, 2004]. Stroke care pathways have the potential to organize care more effectively, although a recent meta-

analysis identified insufficient good quality evidence and so could not support their routine implementation. Pathways may reduce in-hospital delays in door to medical department time, door to imaging time [Suzuki, 2004; Mehdiratta, 2006], door to needle time [Mehdiratta, 2006] and, in case of endovascular treatment, in door to arteriography time.

Stroke patients should be medically assessed as a priority. While only a minority present in an immediately life-threatening condition, many have significant physiological abnormalities or comorbidities. Symptoms and signs which may predict later complications such a space-occupying infarction or bleeding, recurrent stroke, and medical conditions such as hypertensive crisis, co-existing myocardial infarction, aspiration pneumonia, cardiac and renal failure must be recognised early. Stroke severity should be assessed by a targeted neurological examination using the National Institutes of Health Stroke Scale by trained staff [Lyden, 1994].

In all Patients	
1	Brain Imaging: CT or MR
2	ECG
3	*Laboratory Tests* Complete blood count and platelet count, prothrombin time or INR, PTT Serum electrolytes, blood glucose CRP or sedimentation rate Hepatic and renal chemical analysis
When Indicated	
4	Extracranial and transcranial Duplex/Doppler ultrasound
5	MRA or CTA
6	Diffusion and perfusion MR or Perfusion CT
7	Echocardiography (transthoracic and/or transoesophageal)
8	Chest X-ray
9	Pulse oxymetry & Arterial blood gas analysis
10	Lumbar puncture
11	EEG

Table 1. Emergency diagnostic tests in acute stroke patients.

Stroke units

A stroke unit consists of a discrete area of a hospital ward that exclusively or nearly exclusively takes care of stroke patients [Stroke Unit Trialists' Collaboration, 2007] and is staffed by a specialist multidisciplinary team. The core disciplines of the team are medical, nursing, physiotherapy, occupational therapy, speech and language therapy and social work [Langhorne, 2002]. The multidisciplinary team should have a specialist interest in stroke management and work in a coordinated way through regular meetings to plan patient care. Programmes of regular staff education and training should be provided [Langhorne, 2002].

All stroke patients require specialist multidisciplinary care delivered in a stroke unit. Selected acute patients will require additional higher technology interventions, in particular thrombolysis and neurointensivist care. Health services need to establish the infrastructure to deliver these interventions to all patients who require them. This has been the subject of recent consensus documents [Alberts, 2005; Leys, 2007] which have defined the component parts of primary and comprehensive stroke centers.

Primary stroke centers (PSC) are defined as centers with necessary staffing, infrastructure, expertise and programs to prove appropriate diagnosis and treatment for most stroke patients. At the same time, some patients with rare disorders, complex stroke and multi-organ diseases may need more specialized care and resources that are not available in PSC.

Comprehensive stroke centers (CSC) are defined as centers with not only necessary staffing, infrastructure, expertise and programs to provide appropriate diagnosis and treatment for most stroke patients, but also with high technology medical and surgical care (new diagnostic and rehabilitation methods, specialized tests, automatic monitoring significant number of physiological parameters, interventional radiology, vascular surgery, neurosurgery).

General stroke treatment

The term 'general treatment' refers to treatment strategies aimed at stabilising the critically ill patient in order to control systemic problems that may impair stroke recovery. There is a consensus that the management of such problems is a central part of stroke treatment [The European Stroke Initiative Executive Committee and the EUSI Writing Committee, 2003; Leys, 2007] and includes respiratory and cardiac care, fluid and metabolic management, blood pressure control, the prevention and treatment of seizures, deep vein thrombosis, pulmonary embolism, dysphagia, aspiration

pneumonia, other infections, pressure ulceration and occasionally management of elevated intracranial pressure. However many aspects of general stroke treatment have not been adequately assessed in randomised clinical trials.

Recommendations

- *Intermittent monitoring of neurological status, pulse, blood pressure, temperature and oxygen saturation is recommended for 72 hours in patients with significant persisting neurological deficits (Class IV, level GCP).*
- *Continuous monitoring is recommended in medically unstable patients with known cardiac disease or arrhythmia, unstable blood pressure, sepsis, cardiopulmonary disease such as heart failure, cardiac arrhythmias (current or previous history), depressed conscious level or severe stroke and reduced oxygen saturation (Class IV, Level GCP).*
- *Oxygen should be administered if the oxygen saturation falls below 95% (Class IV, level GCP).*
- *Regular monitoring of fluid balance and electrolytes is recommended in patients with severe stroke or swallowing problems (Class IV, Level GCP).*
- *Normal saline (0.9%) is recommended for fluid replacement during the first 24 hours after stroke (Class IV, Level GCP).*
- *Routine blood pressure lowering is not recommended following acute stroke (Class IV, Level GCP).*
- *Cautious blood pressure lowering is recommended with extremely high values (>220/120mm Hg) on repeated measurements (Class IV, Level GCP).*
- *Blood pressure lowering may be required with severe cardiac failure, aortic dissection, hypertensive encephalopathy (Class IV, Level GCP).*
- *Abrupt blood pressure lowering should be avoided (Class II, Level C).*
- *Low blood pressures secondary to hypovolemia or associated with neurological deterioration in acute stroke should be treated with volume expanders (Class IV Level GCP).*
- *Monitoring serum glucose levels is recommended (Class IV, Level GCP)*
- *Treatment of serum glucose levels above 10 mmol/l with insulin titration is recommended (Class IV, Level GCP).*
- *Pyrexia (temperature >37.5°C) should promote a search for concurrent infection (Class IV, Level GCP).*
- *Treatment of pyrexia (temperature >37.5°C) with paracetamol and fanning is recommended (Class III, Level C).*
- *Antibiotic prophylaxis is not recommended in immunocompetent patients (Class II, Level B).*

Diagnostics

Acute stroke is an emergency and stroke victims should have a clear priority for brain imaging compared to other patients, because time limits are so crucial. Rapid, focussed neurological assessment assists considerably in determining which imaging technique is likely to be most helpful and to tailor the individual imaging examination. In patients with stroke, diagnostic brain imaging must be performed immediately on arrival at a hospital so that treatment can be started immediately. Investigation of TIA is equally urgent, because up to 10% of these patients will suffer stroke within the next 48 hours. Immediate access to imaging on arrival at hospital is facilitated by pre-hospital notification and good communication with the imaging facility: stroke services including the ambulances should work closely together with the imaging department to plan best use of resources. Imaging tests should take into account the patient's condition, for example a substantial proportion (up to 45%) of patients with severe stroke may not tolerate MR examination because of their medical condition and contraindications [Schramm, 2004; Barber, 2005; Hand, 2005].

Imaging of the brain and supplying vessels is crucial in the assessment of patients with stroke and transient ischaemic attacks (TIA). Brain imaging distinguishes ischaemic stroke from intracranial haemorrhages and stroke mimics, identifies the type and often also the cause of stroke, may help to differentiate irreversibly damaged tissue from areas that may recover thus guiding emergency and subsequent treatment, and may help to predict outcome. Vascular imaging may identify the site and cause of arterial obstruction, and identifies patients at high risk of stroke recurrence for specific preventions.

Plain CT is widely available, reliably identifies most stroke mimics, and distinguishes acute ischaemic from haemorrhagic stroke within the first five to seven days [Wardlaw, 2003; Kidwell, 2004]. Immediate CT scanning is the most cost-effective strategy for imaging acute hospital-admitted stroke patients [Wardlaw, 2004]. CT is not sensitive for old haemorrhage. Overall, CT is less sensitive, but as specific, for early ischaemic changes as MRI. Two thirds of patients with moderate to severe stroke have visible ischaemic changes within the first few hours of stroke [von Kummer, 2001; Barber, 2000; Wardlaw, 2005; Chalela, 2007], no more than 50% of patients with minor stroke have a visible relevant ischaemic lesion on CT, especially within the first few hours of stroke. Training in identification of early ischaemic changes on CT [Wardlaw, 2005; von Kummer, 1998], and the use of scoring systems [Barber, 2000] improves detection of early ischaemic changes. Some centres prefer to use MRI as first line routine investigation

for acute stroke. It has the advantage that it can identify early ischaemic changes with diffusion weighted sequences (DWI) with higher sensitivity than CT. The higher sensitivity of MRI is particularly useful in diagnosis of posterior circulation stroke and lacunar or small cortical infarctions. It can also detect small and old haemorrhages with T2* (gradient echo) sequences [Dimigen, 2004]. However, DWI can be negative in patients with definite stroke [Ay, 2002].

The degree of restricted water diffusion in the DWI lesion can be quantified by measuring the apparent diffusion coefficient (ADC). Restricted diffusion on DWI is not 100% specific for ischaemic brain damage because hyperintensities may be seen in other conditions, e.g. in epileptic fits, in MS, encephalitis, hypoglycaemia. DWI high signal can be seen in the presence of T2-high signal lesions as 'shine through'. In such cases, examination of ADC maps will show that diffusion is not restricted.

Carotid ultrasound can visualise well the carotid bifurcation and proximal internal carotid artery (ICA) stenosis and can determine the degree of stenosis and plaque characteristics. MRA and CTA can also visualise carotid stenosis well. Systematic reviews and individual patient data meta-analysis indicate that contrast enhanced MRA (CE-MRA) is the most sensitive and specific of the non-invasive imaging modalities for carotid artery stenosis, closely followed by Doppler ultrasound, and then CTA and lastly non-contrast MRA [Wardlaw, 2006]. Transcranial Doppler (TCD) ultrasound allows flow velocity recordings from intracranial vessels and detection of stenosis. A disadvantage is that up to 20% of acute stroke patients do not have an adequate acoustic window particularly in elderly individuals and certain ethnic groups, such as black individuals [Postert, 1997]. The problem can be considerably reduced by using ultrasound contrast agents [Droste, 1999; Droste, 2000]. The combination of ultrasound imaging techniques and MRA reveals excellent results equal to DSA [Niederkoorn, 2003].

All acute stroke and TIA patients should have a 12 channel-ECG. Cardiac monitoring should be conducted routinely after an acute cerebro-vascular event to screen for serious cardiac arrhythmias. For stroke and TIA patients seen after the acute phase, 24 hour Holter ECG monitoring should be performed when arrhythmias are suspected and no other causes of stroke are found.

There is controversy about the indications for, and type of, echocardiography in stroke and TIA patients. TTE is sufficient for patients with ventricular pathology. TEE is superior to TTE in evaluation of the aortic arch, left atrium, and atrial septum. CT and MRI show promise in cardiac evaluation.

Recommendations

1. *In patients with suspected TIA or stroke, urgent cranial CT (Class I) or alternatively MRI (Class II) is recommended (Level A).*
2. *If MRI is used, the inclusion of DWI and a T2*-weighted gradient echo sequences are recommended (Class II, Level A).*
3. *In patients with suspected TIA or stroke, urgent vascular imaging (ultrasound, CTA, or MRA) is recommended (Class I, Level A).*
4. *Patients with TIA, minor stroke, or early spontaneous recovery immediate diagnostic work-up including imaging is recommended (Class I, Level A).*
5. *Perfusion imaging with CT or MRI or the mismatch concept is currently a research tool and cannot be recommended for routine treatment decisions.*
6. *In patients with acute stroke and TIA, early evaluation of physiological parameters, routine blood tests, and ECG is recommended (Class I, Level A).*
7. *Continuous ECG recording is recommended for ischaemic stroke and TIA patients. (Class I, Level A).*
8. *Echocardiography is recommended in selected patients (Class III, Level B).*

Specific stroke treatment

Thrombolytic therapy with recombinant tissue plasminogen activator (tPA; 0.9 mg/kg body weight, max. 90 mg) given within 3 h after stroke onset to patients with acute ischemic stroke significantly improves outcome [The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995], with an NNT of 7 patients to achieve a favorable clinical outcome after 3 months. ECASS and ECASS II tested a 6-hour time window and did not show statistically significant superiority of tPA for the primary endpoints [Hacke, 1998; Hacke, 1995]. A pooled analysis of individual data of the tPA trials showed that even within a three-hour time window the sooner the treatment is initiated the better the outcome (0-90 min: OR 2.11, 95% CI 1.33-3.55; 90-180 min: OR 1.69, 95% CI 1.09-2.62) [Hacke, 2004]. This analysis suggested a benefit up to 4.5 hours.

Finally, in 2008 the ECASS-3 study has provided new data on systemic thrombolysis with rtPA in a time window of 3 to 4.5 hours after stroke onset (27). This multicenter, randomized, placebo controlled, prospective study enrolled over 800 patients to either systemic treatment with rtPA or placebo within 3 to 4.5 hours after stroke symptom onset. Persons older than 80 years, those with a baseline NIHSS score >25, those taking oral anticoagulants, and those who had the combination of a previous stroke and diabetes mellitus were excluded from participation. Symptomatic intracranial hemorrhage, as defined by the criteria used in the NINDS study, was diagnosed in 7.9% of subjects treated with rtPA and 3.5% when given placebo (OR 2.38, 95% CI

1.25 to 4.52, $P<0.006$). However, this increased incidence of hemorrhage is consistent with other clinical rtPA-trials (3, 6, 8, 28-29). The frequency of the primary efficacy outcome in ECASS-3 (defined as mRS score of 0 to 1 at 90 days after treatment) was significantly greater with rtPA (52.4%) than with placebo (45.2%; OR 1.34, 95% CI 1.02 to 1.76; risk ratio 1.16, 95% CI 1.01 to 1.34; $P<0.04$). The number needed to treat to achieve the primary efficacy outcome was 14. Mortality in the two ECASS-3 treatment groups did not differ significantly, although it was nominally higher among the subjects treated with placebo [Hacke *et al.*, 2008].

Thrombolytic therapy appears to be safe and effective across various types of hospitals, if the diagnosis is established by a physician with stroke expertise, and a CT of the brain is assessed by a physician with expertise in reading this imaging study [Hill, 2005][Bateman, 2006][Wahlgren, 2007]. Risks and benefits of tPA should be discussed whenever possible with the patient and family before treatment is initiated.

Blood pressure must be below 185/110 mmHg before, and for the first 24 hours after thrombolysis. High blood pressure management according to the NINDS trial is required [The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995]. Protocol violations are associated with higher mortality rates [Katzan, 2003][Graham, 2003].

The European license for rtPA is restricted to patients between 18 years and 80 years of age. An increasing number of stroke patients are older than 80 years, mainly due to demographic development.

Three-month mortality was higher in patients aged >80 years compared to patients <80 years. Favorable outcome (mRS ≤1) and intracranial hemorrhage (asymptomatic, symptomatic, or fatal) were similarly frequent in both groups. Stroke severity, time to thrombolysis, glucose level, and history of coronary heart disease independently predicted outcome, whereas age did not (48).

The overall rate of hemorrhagic complications after rtPA treatment for ischemic stroke in octogenarians was 6.9%, compared to 5.3% in younger patients ($p = 0.61$). Baseline imaging method (CT or MRI) had no significant influence on ICH, mortality or on favourable outcome on the mRS after 3 months (52).

Intraarterial and combined (IV+IA) thrombolysis

Intra-arterial thrombolytic therapy of proximal MCA occlusion using pro-urokinase in a 6-hour time window was significantly associated with better outcome in a RCT (PROACT II) [Furlan, 1999]. Pro-urokinase is not available and the use of intra-arterial tPA or any other thrombolytic agent is not substantiated by RCTs but by some observational data [Nedeltchev, 2006].

Intra-arterial treatment of acute basilar occlusion with urokinase or tPA, although available for more than 20 years with encouraging results from observational studies [Brandt, 1996][Hacke, 1988], has not been tested in a RCT. In acute basilar occlusion one trial included 16 patients but was underpowered. A systematic review including 420 patients with BA occlusion compared intravenous to intra-arterial thrombolysis and found no significant difference between the two treatment options (43).

A prospective registry (Basilar Artery International Cooperation Study, BASICS) investigated 592 patients with acute BA occlusion for differences regarding antithrombotic therapy, intravenous or intra-arterial thrombolysis. However, most patients received intra-arterial thrombolysis. No statistically significant superiority for intra-arterial over intravenous thrombolysis was found. Therefore, unequivocal superiority of intra-arterial over intravenous thrombolysis is not shown.

The so-called 'bridging concept' is currently preferred in most centers in case of proven vessel occlusion. Therefore rtPA is given with 60% of the full recommended dosage as first-line treatment and – in case of non-responders – either local application of rtPA at the thrombus site, use of mechanical recanalization devices, mechanical clot disruption, or a combination of the aforementioned techniques is performed. Standard-treatment of patients with BA occlusion in non-specialized centers or where neuroradiological intervention is not available, should be intravenous application of rtPA, since there are no trials to support the superiority of intra-arterial thrombolysis in patients with BA occlusion.

Intra-arterial recanalization devices

In the Mechanical Embolus Removal in Cerebral Embolism (MERCI) trial, vessels were opened with a device that removed the thrombus from an intracranial artery. Recanalization was achieved in 46% (69/151) of patients on intention to treat analysis, and in 48% (68/141) of patients in whom the device was deployed within 8 hours of the onset of stroke symptoms [Smith, 2005 #501]. No RCTs with outcome data are available for any recanalization devices.

A randomized trial of standard intravenous tPA as compared with a combined intravenous and intra-arterial approach has started after encouraging phase II results (IMS3) [IMS investigators, 2007].

Anti-platelet therapy

The results of 2 very large randomized, non-blinded intervention studies indicate that aspirin started within 48 h after stroke (International Stroke

Trial, Chinese Acute Stroke Trial) is safe and effective [International-Stroke-Trial-Collaborative-Group, 1997; CAST-Collaborative-Group, 1997]. In absolute terms, 13 more patients were alive and independent at the end of follow-up for every 1000 patients treated. Furthermore, treatment increased the odds of making a complete recovery from stroke (OR = 1.06; 95% CI 1.01 to 1.11). In absolute terms, 10 more patients made a complete recovery for every 1000 patients treated. Antiplatelet therapy was associated with a small but definite excess of 2 symptomatic intracranial haemorrhages for every 1000 patients treated, but this was more than offset by a reduction of 7 recurrent ischemic strokes and about one pulmonary embolus for every 1000 patients treated.

Brain oedema

Space-occupying brain oedema is a main cause of early deterioration and death in patients with large supratentorial infarcts. Life-threatening brain oedema usually develops between the 2nd and 5th day after stroke onset, but up to a third of patients can have neurological deterioration already within 24 hours after symptom onset [Hacke Qureshi, 2003].

Medical therapy in patients with large space-occupying infarctions and brain oedema is based mostly on observational data. Basic management includes head positioning at an elevation of up to 30°, avoidance of noxious stimuli, pain relief, appropriate oxygenation and normalizing body temperature. If ICP monitoring is available, cerebral perfusion pressure should be kept above 70 mmHg [Unterberg, 1997]. Osmotherapy with glycerol 10% usually given intravenously (4 x 250 ml of 10% glycerol over 30-60 min) or intravenous mannitol 25-50 g every 3-6h is the first medical treatment to be used if clinical or radiological signs of space-occupying oedema occur [Righetti, 2002][Bereczki, 2001]. Hypertonic saline solutions given intravenously are probably similarly effective [Schwarz, 2002]. Hypotonic and glucose-containing solutions should be avoided as replacement fluids. Dexamethasone and corticosteroids are not useful for brain oedema treatment after stroke [Qizilbash, 2002 #143]. Thiopental given as a bolus can quickly and significantly reduce ICP, and be used to treat acute crises. Barbiturate treatment requires ICP and EEG monitoring and careful monitoring of haemodynamic parameters, as a significant blood pressure drop may occur.

Decompressive surgery

Malignant MCA infarction: The pooled analysis of 93 patients included in 3 European RCTs (DECIMAL, DESTINY, HAMLET) showed that more patients in the decompressive-surgery group than in the control group

had a mRS ≤4 (75% vs. 24 %; NNT 2), a mRS ≤3 (43% vs. 21%, NNT 4), and survived (78% vs. 29%; NNT 2) after one year [Vahedi, 2007]. There was no increase in the proportion of patients who survived surgery in a vegetative stage (mRS 5). Inclusion criteria for this combined analysis were age 18-60 years, NIHSSS >15, decrease in level of consciousness to a score of 1 or greater on item 1a of the NIHSS, infarct signs on CT of 50% or more of the MCA territory or >145 cm3 on dw-MRI, and inclusion <45 hours after onset (surgery <48 hours). Follow-up of survival and functional status beyond 1 year is currently ongoing in the DECIMAL and DESTINY.

Cerebellar Infarction: Ventriculostomy and decompressive surgery are considered treatments of choice of space-occupying cerebellar infarctions, although RCTs are lacking. Like in space-occupying supratentorial infarction, the operation should be performed before signs of herniation are present. The prognosis among survivors can be very good, even in comatose patients prior to operation.

Recommendations

- *Intravenous tPA (0.9 mg/kg BW, maximum 90 mg), with 10% of the dose given as a bolus followed by an infusion lasting 60 min, is recommended within 3h of onset of ischemic stroke (Class I, level A).*
- *Intravenous tPA may be of benefit also for acute ischemic stroke beyond 3 h after onset (Class I, level B) but is not recommended in clinical routine. The use of multimodal imaging criteria may be useful for patient selection (Class III, level C).*
- *Blood pressure higher than 185/110 mmHg must be lowered before thrombolysis (Class IV, level GCP).*
- *Intravenous tPA may be used in patients with seizures at stroke onset, if the neurological deficit is related to acute cerebral ischemia (Class IV, level GCP).*
- *Intravenous tPA may also be administered in selected patients over 80 years of age (Class III, level C) although this is outside the current European label.*
- *Intra-arterial treatment of acute MCA occlusion in a 6-hour time window is an option (Class II, level B).*
- *Intra-arterial thrombolysis is recommended for acute basilar occlusion in selected patients (Class III, level B). Intravenous thrombolysis for basilar occlusion is an acceptable alternative even after 3 h (Class III, level B).*
- *ASA (160-325 mg loading dose) should be given within 48 h after ischemic stroke (Class I, level A).*
- *If thrombolytic therapy is planned or given ASA or other antithrombotic therapy should not be initiated within 24 h (Class IV Level GCP).*
- *The use of other antiplatelet agents, single or combined, is not recommended in the setting of acute ischemic stroke (Class III, Level C).*

- *The administration of GP IIb-IIIa inhibitors therapy is not recommended (Class I, level A).*
- *Early administration of UFH, low molecular weight heparin or heparinoids is not recommended for the treatment of patients with ischemic stroke (Class I, level A).*
- *Currently, there is no recommendation to treat ischemic stroke patients with neuroprotective substances (Class I, level A).*

Summary

The outcome of patients who suffered an ischemic stroke has massively improved over the last decades. Mortality rates are down and the number of patients who will fully recover has increased. Still there are unfortunate cases who survive in a very poor state, bur their number also decreases. This all is due to Stroke Unit Care, rapid referral to expert centers, thrombolysis, expert general therapy, multidisciplinary teams and critical care facilities.

This is the good news. On the other side, the incidence rates of stroke are expected to explode over the next few decades. With all the great advances in acute stroke care and the management networks that are evolving, the number one priority must be education and prevention.

For the extensive list of references please refer to the free access download of the article on the ESO-website (eso-stroke.org).