

Consensus Statement on Diagnosis and Treatment of Acute Ischemic Stroke

Stroke Council - Argentine Society of Cardiology

Director of the Consensus

Ana María Atallah, M.D.

Secretary

María Cristina Zurrú, M.D.

Authors

Claudia Alonzo, M.D.
 Sebastián Ameriso, M.D.
 Ana María Atallah, M.D.
 Juan José Cirio, M.D.
 María Cristina Zurrú, M.D.

Stroke Council

Director

María Cristina Zurrú, M.D.

Academic Secretary

Rafael García Dávila, M.D.

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 Fabiana Ortega, M.D.
 Gabriela Orzuza, M.D.
 Martín Pedersoli, M.D.
 Gabriel Persi, M.D.
 Ricardo Romero, M.D.

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INTRODUCTION

This consensus of experts was made to provide management recommendations during the first 6 hours after an ischemic stroke. A systematic review of the literature published in the Medline database from January 1965 to June 2011 was performed. The collected information was classified following the American Heart Association guidelines to establish the Level of Evidence (Appendix 1). In the absence of clinical trials to account for indications, recommendations were based on expert opinion, taking into account Good Clinical Practice Guidelines (GCPG). Applicability of these recommendations was evaluated according to the 2005 Directions for the Adaptation of Clinical Practice Guidelines of the Epidemiological Research Institute of the National Academy of Medicine in Argentina, which considers a range from 1 to 7 to establish applicability according to the following parameters: organization and operation of the health care system, population needs, costs, resources availability, beliefs, values of the target population, and equity (Appendix 2). (1)

Stroke is a serious public health issue in Argentina, producing a significant burden of disease in terms of healthy life-years lost due to disability and premature death. According to data provided by the World Health Organization, 15 million people are affected every year by cerebrovascular diseases out of which one third dies and another third is permanently disabled. (2) Stroke is the second cause of death and the first cause of disability in the adult population. (3, 4) There is only one study on the prevalence of cerebrovascular disease in Argentina, conducted in the city of Junín, with 79.6% ischemic events and 20.4% hemorrhagic reported events. Point prevalence ratio was 868.1 cases per 100000 inhabitants (473.4/100000 rate adjusted to the worldwide population). In both sexes, prevalence increased with age, and significant disability was reported in 52% of the cases. (5) Two hospital registries in Argentina provided data on the most prevalent vascular risk factors, the type of events, and the implementation of fibrinolytic therapy in ischemic stroke. The first registry was the ARENAS study, conducted for six months by the Stroke Council of the Argentine Society of Cardiology, with the participation of 84 centers throughout the country, including data from 1235 patients. The major risk factor was arterial hypertension (78.5%), followed by history of heart disease (34%), smoking (32%), dyslipidemia (31%), previous stroke (22%), diabetes (17%), and atrial fibrillation (15%). (6)

The second epidemiological registry was the ReNACer study, conducted by the Argentine Neurological Society. It enrolled a total of 1991 patients with stroke in 74 public and private hospitals; 83% were ischemic and 17% hemorrhagic events, and the major risk factor was arterial hypertension (81.6%). (7)

2. INITIAL ASSESSMENT OF THE PATIENT WITH ISCHEMIC STROKE

The concept "time is brain" expresses that stroke treatment should be considered a medical emergency. Therefore, avoiding delays should be the main purpose of prehospital care. This has far-reaching consequences in terms of detecting the signs and symptoms secondary to the vascular event, both for patients and their families or companions, as well as in the nature of the first medical contact or in how patients are transported to the hospital. While many people acknowledge that stroke is an emergency and that consequently they would seek immediate medical care, in fact only 50% calls the emergency medical services. In general, as reported by several studies, the first contact is made by a family member or a general practitioner in up to 48% of the cases. (8, 9)

Only about 33-50% of the patients are aware of their symptoms as indicative of stroke. There are significant differences between theoretical knowledge and reaction in case of suffering an acute event. Some studies have shown that patients with better knowledge of stroke symptoms do not always get to the hospital earlier. (8 -11)

In the hospital, acute stroke care should include the Emergency Medical Services (EMS) and the Department of Neurology or the Stroke Unit. Communication and collaboration among emergentologists, neurologists, intensivists, radiologists, and lab staff are important to facilitate prompt treatment. (9, 12, 13) Those centers where a Stroke Unit or a specialized on duty staff are not available should train EMS physicians to evaluate and manage these patients and, administer thrombolysis if necessary. (11) The EXPRESS study showed that early initiation of treatment was associated with 80% reduction in the risk of recurrent vascular events. (14)

There should be Clinical Practice Guidelines for acute care of stroke patients, as centers using these guidelines achieve higher rates of thrombolysis interventions. (13) Ongoing implementation of schemes to improve quality of care may reduce intrahospital delays. (15) Efficacy goals should be defined and measured for each institution; as a minimum requirement, door-to-neuroimaging and door-to-needle times should be monitored.

A neurologist or cerebrovascular disease specialist should be available at the emergency room for the acute care of stroke patients. Comparing the neurological as opposed to the non-neurological care, two studies in the United States showed that although neurologists

perform more extensive and expensive tests, patient hospital stay is shorter, mortality rate is lower at 90 days, and functional status at discharge improves. (16) The EMS organization may help avoid delays and unnecessary intra-hospital transportations. (17)

While only a small number of stroke patients show imminent vital risk, many of them have significant comorbidities or physiological changes. Signs and symptoms that predict complications, such as malignant cerebral infarction with mass effect, hemorrhagic transformation, recurrent events, or coexisting medical conditions as hypertensive crisis, myocardial infarction, aspiration pneumonia, and heart or renal failure, should be promptly detected. Severity of ischemic stroke should be determined by a physician trained in the use of the NIHSS scale (National Institutes of Health Stroke Scale). (18) Neuroimaging facilities should be placed within or close to the EMS. Neuroradiologists should be called as soon as possible.

Initial examination should include (8, 9):

1. Appropriate airway protection, breathing pattern, and pulse oxygen saturation > 92 %.
2. Assessment of blood pressure (BP) and heart rate and prevention of arterial hypotension to maintain proper perfusion pressure.
3. Evaluation of neurological deficit.
4. Evaluation of concomitant heart disease and continuous electrocardiographic monitoring to assess arrhythmias or signs of myocardial ischemia.

At the same time, blood samples should be withdrawn for coagulation and basic biochemical tests. Examination should be completed with a clinical history including vascular risk factors, medications, conditions predisposing hemorrhage complications, and presence of conditions that may simulate a stroke, as for example, epilepsy or hypoglycemia, among others. Moreover, a detailed history of drug abuse, use of oral contraceptives, infection, trauma, or migraine may be useful to provide presumptive diagnoses, mainly among young patients.

Recommendations

- All stroke patients should be treated in a Stroke Unit or at the EMS by trained staff (Class I, Level of Evidence B).
- Health care systems should ensure stroke patients the accessibility to high-technology medical and surgical care when necessary (Class I, Level of Evidence B).
- The development of clinical networks, including telemedicine, is promoted to expand the access to specialized and high-technology medical care (Class II, Level of Evidence B).

3. CLINICAL ASSESSMENT SCALES

On the neurological evaluation, the possibility of stroke should be initially considered. At the

prehospital level, the Cincinnati or the LAPSS (Los Angeles Prehospital Stroke Screen) stroke scales are generally used. These scales have shown a sensitivity > 87 % and a specificity of 60 % for the diagnosis of stroke (Tables 1 & 2). (19, 20). The NIHSS scale, which reduces the variability among different observers, is used to determine neurological deficit in the hospital stage (Table 3). The management of this scale requires training and certification. Several studies have shown an appropriate correlation with patient clinical outcome, helping to determine a proper selection of fibrinolytic therapy. (21)

At discharge, disability, daily life activities, and quality of life scales are used. The modified Rankin scale, Barthel index, SF-36, or EuroQOL are generally used. (22)

Recommendations

- Use screening scales at prehospital stage to identify patients with possible stroke diagnosis. (Class I, Level of Evidence B).
- Apply the NIHSS scale to quantify the neurological deficit and subsequent patient follow-up. (Class I, Level of Evidence B).

Table 1. Cincinnati Stroke Scale

Facial	Asymmetry	Smile, show teeth
Motor	Deficit	Raise arms with palms up
Language	Speech	Ask to repeat words

Table 2. Los Angeles Prehospital Stroke Screen (LAPSS)

Criteria	Yes	No	Unknown
Age > 45 years			
No prior history of seizures or epilepsy			
Symptoms duration < 24 hours			
Patient in wheelchair or bedridden			
Blood glucose < 50 or > 400 mg/dl			
Asymmetries			
Facial			
Grip			
Arms			

Table 3. NIHSS Score (National Institutes of Health Stroke Scale)

<p>1a Level of consciousness</p> <p>0 = alert 1 = drowsy 2 = no response</p>	<p>4 Facial palsy</p> <p>0 = normal 1 = minor paresis 2 = partial paresis 3 = total paresis</p>	<p>7 Ataxia</p> <p>0 = absent 1 = present in one limb 2 = present in both limbs</p>
<p>1b Questions</p> <p>0 = answers both questions correctly 1 = answers only one question correctly 2 = answers neither question correctly</p>	<p>5a Motor arm - left</p> <p>0 = no drift 1 = drifts down before 10 seconds 2 = drifts down before 10 seconds 3 = no effort against gravity 4 = no movement</p>	<p>8 Sensory</p> <p>0 = normal 1 = mild loss 2 = severe loss</p>
<p>1c Commands</p> <p>0 = obeys correctly both commands 1 = obeys only one command correctly 2 = obeys neither command correctly</p>	<p>5b Motor arm - right</p> <p>0 = no drift 1 = drifts before 10 seconds 2 = falls before 10 seconds 3 = no effort against gravity 4 = no movement</p>	<p>9 Language</p> <p>0 = normal 1 = mild aphasia 2 = severe aphasia 3 = global aphasia</p>
<p>2 Gaze</p> <p>0 = normal 1 = partial gaze palsy 1 = total gaze palsy</p>	<p>6b Motor leg - right</p> <p>0 = no drift 1 = drifts before 5 seconds 2 = falls before 5 seconds 3 = no effort against gravity 4 = no movement</p>	<p>10 Dysarthria</p> <p>0 = normal 1 = mild 2 = severe</p>
<p>3 Visual field</p> <p>0 = no visual loss 1 = partial hemianopia 2 = complete hemianopia 3 = bilateral hemianopia</p>	<p>6b Motor leg - right</p> <p>0 = no drift 1 = drifts before 5 seconds 2 = falls before 5 seconds 3 = no effort against gravity 4 = no movement</p>	<p>11 Extinction and Inattention</p> <p>0 = normal 1 = mild 2 = severe</p>

4. IMAGING IN ISCHEMIC STROKE

On admittance, patients suspected of stroke should have general and neurological examinations, followed by a neuroimaging study to begin treatment as soon as possible. The evaluation for transient ischemic attack is also crucial, because up to 10% of the patients will suffer an ischemic stroke in the next 48 hours. Immediate access to neuroimaging is facilitated by prehospital notification and by the proper coordination between the EMS and the neuroimaging department for adequate use of resources. (23-25)

The diagnostic neuroimaging procedure must be sensitive and specific for stroke detection, particularly in the early phase, with reliable and technically feasible images in patients with an acute event. (26, 27) A focused and immediate neurological examination helps determine the imaging technique to be used. Imaging tests should take into account the patient's general condition; for instance, up to 45% of patients with severe stroke may not tolerate a magnetic resonance imaging (MRI) due to their clinical condition and/or to contraindications. (28)

Patients admitted with less than 4 or 5 hours after symptom onset are candidates to thrombolytic therapy; a computed tomography scan (CT) is often enough to guide routine thrombolysis. (29, 30) Late admitted patients may be candidates for clinical trials to assess the extension of the therapeutic window for thrombolysis or other experimental reperfusion strategies. (31, 32)

CT is widely available to identify most conditions mimicking cerebrovascular events, and differentiates acute ischemia from intracerebral hemorrhage within the first 5 to 7 days. Immediate CT scan is the most cost-effective strategy to study acute stroke patients, but it is not sensitive for old hemorrhages. (33) Two thirds of the patients with moderate to severe stroke have visible ischemic signs within the first hours, but less than 50% of the patients with minor stroke have a visible, relevant ischemic lesion on CT, especially within the first hours of the event. (34-36) Training on CT identification of early ischemic signs and use of scoring systems improve stroke detection (Figure 1). Early signs are: blurring of the internal capsule, attenuation of the lentiform nucleus, loss of cortical gray matter and underlying white matter differentiation, such as blurring of the insular ribbon, and mild sulcal effacement. These findings are observed in 80% of the patients with occlusion of a major vessel within the first 6 hours after stroke. (37-39) Hyperattenuation of the middle cerebral artery, or string sign, is suggestive of intraluminal thrombus, but it can also be visualized in patients with calcified atheroma of this artery without indicating thrombosis. (40-42)

The presence of early signs of ischemia on CT should not exclude patients from thrombolysis within the first 3 hours, even though patients with a hypoattenuating lesion exceeding one third of the

middle cerebral artery (MCA) territory may benefit less from thrombolysis and present higher bleeding risk. (43, 44)

Some centers prefer to use MRI as the first-line neuroimaging technique for acute ischemic stroke. MRI with diffusion-weighted imaging has a higher sensitivity to detect early ischemic changes than CT scan. This higher sensitivity is particularly useful in the diagnosis of cortical, cerebellar and/or lacunar infarctions. MRI can also detect small or old hemorrhages for a prolonged period using T2* gradient echo sequences. However, diffusion may be negative in patients with definitive ischemic stroke. (45-47) Restricted diffusion, measured by the apparent diffusion coefficient, is not 100% specific for ischemic brain damage detection. Altered diffusion is not equivalent to permanently damaged tissue, since although a damaged tissue on altered diffusion often proceeds to stroke, recovery is possible. (48-50) Tissues with modest reductions of the apparent diffusion coefficient values may be permanently damaged; so far, there is no reliable threshold to differentiate dead from the still viable tissue. Other MRI sequences (T2, FLAIR, T1) are less sensitive for the early detection of ischemic brain damage. MRI is important to assess acute stroke patients with unusual presentation, certain ischemic stroke varieties, and uncommon etiologies, or when there is suspicion of a stroke mimicking event which is not clarified by CT. If arterial dissection is suspected, neck MRI with fat suppressed T1-weighted sequences should be required to detect intramural hematoma. (45, 46)

MRI is less suited for agitated patients or with vomiting or aspiration risk. If necessary, emergency life support should be continued during imaging as patients (especially those with severe stroke) may become hypoxic while in the supine position. Aspiration risk is increased in patients who are unable to protect their airway. (45)

Perfusion imaging with CT or MRI and angiography may be used in selected patients with ischemic stroke, as in those with an unclear time window,

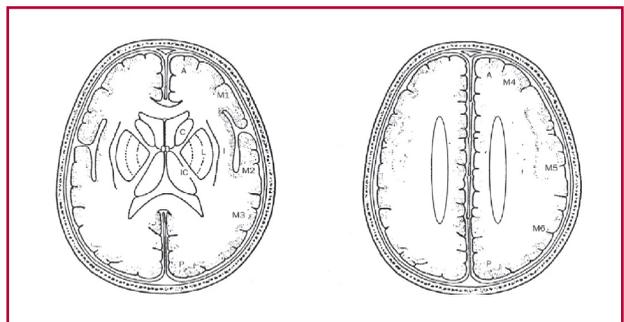


Fig. 1. ASPECTS Score. CT cuts through the basal ganglia and the corona radiata rated with ASPECTS. A point is taken off for each affected area.

or late admission, to aid on thrombolysis therapy decision making, although there is no clear evidence that patients with particular perfusion patterns are more or less likely to benefit from thrombolysis. Selected patients with intracranial arterial occlusion may be candidates for intra-arterial thrombolysis, although scientific evidence is limited. Patients with combined obstructions of the internal carotid artery (ICA) and MCA have less possibility of recovery with intravenous thrombolysis than patients with isolated MCA obstructions. (49, 50) In patients with main MCA occlusion, the frequency of extracranial carotid occlusive disease is significantly high.

Mismatch between the volume of critically hypoperfused brain tissue (which can recover after reperfusion) and the volume of infarcted tissue (which does not recover even with reperfusion) may be detected with MR diffusion/perfusion imaging with moderate reliability, but this is not yet a proven strategy to improve thrombolysis response up to 9 hours. (51) There is disagreement on how to best identify irreversible ischemic brain injury and define critically impaired blood flow. Quantification of MRI perfusion is problematic, and there are diverse associations between perfusion parameters and clinical and radiological results. (52) Decreases in cerebral blood flow in CT are associated with subsequent tissue damage, but the therapeutic value of CT perfusion imaging has not yet been established. Although infarct expansion may occur in a high proportion of patients with mismatch, up to 50% of the patients without unbalanced perfusion-diffusion may also have infarct growth and so might benefit from tissue salvage. Hence, neither CT or MRI perfusion imaging nor the mismatch concept can be recommended for routine therapy decision making. (53-60)

Microhemorrhages are present on T2* weighted gradient MRI in up to 60% of the patients with hemorrhagic stroke, and are associated with older age, hypertension, diabetes, leukoaraiosis, lacunar stroke, and amyloid angiopathy. In acute ischemic stroke patients, the incidence of symptomatic intracranial hemorrhage following thrombolysis was not increased when cerebral microbleeds on pre-treatment T2*-weighted MRI were present. (50, 51)

Vascular imaging should be promptly performed to identify patients with significant symptomatic arterial stenosis who could benefit from endarterectomy or angioplasty. Non-invasive imaging with color-coded duplex imaging of the extracranial and intracranial arteries, CT angiography, or contrast-enhanced MR angiography (CE-MRA) is widely available. These approaches are relatively risk-free, whereas intra-arterial angiography currently has a 1% lower risk of causing embolism in patients with symptomatic carotid lesions. (61, 62) Invasive angiography may be necessary in certain circumstances, for example, when other explorations have not been conclusive.

Recommendations

- In patients with suspected TIA or stroke, urgent CT scan should be performed (Class I, Level of Evidence A), or alternatively, MRI (Class II, Level of Evidence A).
- If MRI is performed, the inclusion of diffusion-weighted imaging, apparent diffusion coefficient (ADC), gradient echo sequences, and FLAIR (Class II, Level of Evidence A) are required.
- In patients with TIA and ischemic stroke, immediate diagnostic work-up is necessary (ultrasound, CT-angiography, or RM-angiography) (Class I, Level of Evidence A).

5. GENERAL MEDICAL TREATMENT OF ISCHEMIC STROKE

The head of the bed should be tilted up at 30-45°, and a nasogastric tube to prevent aspiration of gastric contents should be inserted in case of consciousness deterioration. Up to 63% of the patients with ischemic stroke develop hypoxemia, which has been related to stroke severity, dysphagia, and age. Monitoring of arterial oxygen saturation and initial oxygen therapy are recommended if pulse oxygen saturation falls below 92%. Patients with airway obstruction or poor management of respiratory secretions may need orotracheal intubation. (63, 64)

Both high blood pressure (BP) levels and low systolic blood pressure (SBP) have been related to a worse prognosis. Early mortality rate increases by 17.9% per each 10 mm Hg below 150 mm Hg in SBP. Different studies with hypotensive drugs have been conducted during the acute phase of ischemic stroke. Today, drugs such as ultra short-acting beta-blockers or angiotensin-converting enzyme inhibitors, which have shown BP reduction without changing cerebral blood flow, are recommended. In brief, treating hypertension during the acute phase should be conducted only in those patients with BP > 200/120 mm Hg in two consecutive measurements separated by a 15 minute interval, provided other factors that may cause hypertension have been ruled out, or in patients with heart failure, aortic dissection, acute myocardial infarction, acute renal failure, pregnancy, or in candidates for thrombolytic therapy. In case of BP modification, a decrease below 15% of the initial value during the first 24 hours is suggested. (63, 64)

Over the last years, several clinical studies have pointed out that hyperglycemia in the acute phase of ischemic stroke would reflect an often unknown pre-existing diabetes mellitus. In these patients, hyperglycemia > 120 mg/dl is a negative prognostic marker regardless of age, severity, and subtype of the event. Moreover, this deleterious effect is greater in non-diabetic patients. At present, strict monitoring of blood glucose levels during the acute phase is recommended, to achieve euglycemia avoiding the administration of dextrose solution, and initiate insulin therapy if blood glucose level is > 180 mg/dl. (63, 64)

Hydration should be performed with normal saline solution, keeping a neutral balance. The use of hypotonic solutions (such as dextrose or Ringer's lactate) may cause cerebral edema and hyponatremia. (63, 64)

Body temperature should be regularly checked, and in case of armpit temperature $> 37.5^{\circ}\text{C}$, antipyretic medication should be administered. In these cases, it is necessary to rule out infection, the most common being aspiration pneumonia or urinary infections.

Oral feeding should be started only after clinical examination to rule out an evident deglutition disorder. In patients with evidence of aspiration pneumonia feeding by tube is necessary. (63, 64)

Voiding dysfunction is a common complication in stroke patients, so it is important to rule out the presence of a distended bladder indicating acute urinary retention.

Patients should be mobilized prematurely to prevent bed sores and abnormal positions that may hinder their rehabilitation. Patients with severe motor deficit who cannot walk during the acute phase should receive doses of heparin to prevent deep vein thrombosis and pulmonary thromboembolism. (63, 64)

Levetiracetam therapy to prevent seizures is not a routine indication for patients with ischemic stroke; only those who have had seizures should receive this therapy. (63, 64)

Recommendations

- Neurological status, heart rate, blood pressure, and oxygen saturation should be monitored in patients with ischemic stroke, an indication based on Good Clinical Practice Guidelines (GCP).
- Oxygen should be administered if the oxygen saturation falls below 92% (GCP).
- Maintain a neutral fluid balance and correct hydro-electrolyte disturbances in patients with ischemic stroke (GCP).
- Use normal saline (0.9%) for hydrotherapy during the first 24 hours after ischemic stroke (GCP).
- As a general rule, blood pressure lowering is not recommended during ischemic stroke (GCP).
- Elevated blood pressure should be lowered in patients with extremely high blood pressure levels ($> 220/120$ mm Hg) on repeated measurements and with clinical evidence of acute myocardial infarction, severe cardiac failure, aortic dissection, pregnancy, renal failure, or hypertensive encephalopathy (GCP).
- Treat with volume expanders low blood pressure secondary to hypovolemia or associated with neurological deterioration during acute ischemic stroke (GCP).
- Monitor serum glucose levels (GCP).
- Treat serum glucose levels > 180 mg/dl with insulin (Class II, Level of Evidence B).
- Correct hypoglycemia (< 50 mg/dl) with

intravenous dextrose or 10-20% glucose infusion (Class II, Level of Evidence B).

- Lower temperature $> 37.5^{\circ}\text{C}$ with paracetamol or physical measures (GCP).
- Search for concurrent infection in case of hyperthermia (GCP).
- Prescribe low-dose heparin to prevent deep vein thrombosis and pulmonary thromboembolism (Class I, Level of Evidence A).
- Routine prophylactic administration of anticonvulsants is not recommended and should only be indicated in patients with a history of seizures (Class II, Level of Evidence B).

6. SPECIFIC MEDICAL TREATMENT OF ISCHEMIC STROKE

Thrombolytic therapy

Intravenous tissue plasminogen activator

Thrombolytic therapy with rtPA (0.9 mg/kg body weight, maximum dose 90 mg) given within 3 hours after onset of ischemic stroke, significantly improves outcome after 3 months, with an absolute increase of 11 to 13% patients who improve with no deficit or with an insignificant impairment according to the study scales. The number needed to treat (NNT) to achieve a favorable clinical outcome after 3 months is 7. A pooled analysis of individual data of rtPA trials showed that, even within a 3-hour window, earlier treatment results in better outcome (0-90 min: OR 2.11; 95% CI 1.33 to 3.55; 90-180 min: OR 1.69; 95% CI 1.09 to 2.62). (65-67)

The meta-analysis of NINDS, ECASS I, ECASS II and Atlantis A and B studies suggests the benefit could extend up to 4.5 hours. (68, 69) This is further confirmed by the ECASS III study, which shows a benefit in patients < 80 years of age, with a NIHSS score < 25 points and with no history of oral anticoagulant agents, previous stroke or diabetes when they were treated within a 3 to 4.5-hour time window (Table 4). (70)

The NINDS (National Institute of Neurological Disorders and Stroke) study showed that the extent of early ischemic changes (using the ASPECT score) had no effect on treatment response within the 3-hour time window. However, European regulatory agencies do not advocate the treatment in patients with severe events (NIHSS ≥ 25), extended early signs of ischemia on CT scan, or age above 80 years (unlike the United States approval). Observational studies suggest that rtPA given within the first 3 hours of the event is safe and effective in patients over 80 years of age, but more randomized data are pending. The effect of gender on the response to rtPA is uncertain. (71)

Thrombolytic therapy appears to be safe and effective across various types of hospitals, if the diagnosis is established by an experienced physician on cerebrovascular disease and the brain CT is also assessed by an experienced physician. Whenever

possible, the risks and benefits of rtPA should be discussed with the patient and the family before treatment is initiated.

Blood pressure must be below 185/110 mm Hg before, and for the first 24 hours after thrombolysis. Management of blood pressure above those values is required. Protocol violation is associated with higher mortality rates (Table 5). (72-74)

Continuous transcranial ultrasound was associated with an increased rate of early recanalization after rtPA in a small randomized trial. This effect may be facilitated by the administration of microbubbles. However, a randomized clinical trial has recently been stopped for undisclosed reasons. (75)

The use of multimodal imaging criteria may be

useful for patient selection. Several large observational studies suggest improved safety and possibly greater efficacy in patients treated with IV rtPA beyond 3 hours based on advanced imaging criteria. However, available data on mismatch, as defined by multimodal MRI or CT, are too limited to guide thrombolysis in routine practice. Patients with seizure at onset of symptoms have been excluded from thrombolytic trials because of potential confusion with postictal convulsive Todd's phenomenon. Case series have suggested that thrombolysis may be used in such patients when there is evidence of an acute ischemic event. (76-78)

Post hoc analyses have identified the following potential factors associated with increased risk of

Table 4. Inclusion and exclusion criteria for rtPA therapy

3-hour Inclusion criteria

- Patients with signs of ischemic stroke of less than 3 hours of evolution.
- Age > 18 years.
- Normal brain CT scan or with signs of acute ischemia in less than 33% of the MCA territory.
- NIHSS 4 to 25.

4.5 hour inclusion criteria

- Patients with signs of ischemic stroke of less than 4.5 hours of evolution.
- Age between 18 and 80 years.
- Normal brain CT scan or with signs of acute ischemia in less than 33% of the MCA territory.
- NIHSS 4 to 25.
- Patient with no history of oral anticoagulant or heparin use.

Exclusion criteria

Absolute

- Intracranial hemorrhage in CT scan
- Evolution of stroke symptoms with unknown time of onset.
- Minor or rapidly improving stroke symptoms before the beginning of infusion.
- NIHSS > 25.
- Symptoms suggestive of subarachnoid hemorrhage, even with normal CT scan.
- Heparin therapy 48 hours prior to the event, or elevated aPTT.
- Ischemic stroke in the last 3 months.
- Platelet count < 100,000.
- Blood glucose < 50 mg/dl or > 400 mg/dl.
- SBP > 185 mm Hg, DBP > 110 mm Hg.
- Known bleeding diathesis.
- Oral anticoagulation therapy. rtPA therapy may be considered if INR < 1.7.
- Recent or evident severe hemorrhage.
- History of intracranial hemorrhage.
- History of subarachnoid hemorrhage due to aneurysm rupture.
- History of central nervous system lesion (aneurysms, neoplasms, spinal intracranial surgery).
- Arterial puncture at a noncompressible site in the last 10 days.
- Bacterial endocarditis and pericarditis.
- Major surgery or serious trauma in the last 3 months.

Relative criteria

- AMI only if patient was treated with rtPA during the last year.
- Pregnancy (first trimester).
- Seizures at stroke onset.
- Diabetes (retinopathy with bleeding).
- History of anaphylaxis due to rtPA.

Administration schedule of rtPA

- A dose of 0.9 mg/kg is administered, the maximum dose being 90 mg.*
- Ten percent of the total dose is administered in a one minute bolus.
- The rest of the dose is administered in a continuous infusion during one hour.
- Recommendations on general treatment and concomitant treatments.
- Heparin, aspirin, or oral anticoagulants will not be administered in the first 24 hours after the event because they may increase the risk for cerebral hemorrhage.
- Patient should be monitored, preferably in an intensive care unit.
- A NIHSS score will be acquired every 15 minutes during infusion, at 2 hours, and at 24 hours, and a 4-point increase (or more) in the NIHSS scale is suggestive of neurological deterioration, in which case a CT scan should be performed immediately.
- Infusion must be stopped if there is clinical suspicion of hemorrhage (severe headache, vomiting, reduced level of conscience, worsening of neurological deficits), and an immediate CT scan will be performed.
- Insert vesical catheter or a nasogastric tube prior to infusion.
- Insert two high-flow peripheral intravenous catheters.
- Avoid arterial punctures.
- If anaphylactic reaction occurs (which is rare), discontinue the infusion and initiate appropriate treatment (corticosteroids, adrenalin, and intubation).
- BP will be monitored every 15 minutes during the first hour of infusion, every 30 minutes during the following 6 hours, and then every hour for 24 hours.

*Note: in Asian patients, a 0.6 mg/kg rtPA dose is suggested due to higher risk of bleeding as a result of drug metabolism. (109, 110)

Table 4. (cont.) Inclusion and exclusion criteria for rtPA therapy

intracerebral hemorrhage complications following rtPA administration (79-80):

- Hyperglycemia.
- History of diabetes.
- NIHSS > 22.
- Age > 80 years.
- Increased time to treatment.
- Previous therapy with aspirin or oral anticoagulant agents.
- History of congestive heart failure.
- Low plasminogen activator inhibitor activity.
- NINDS protocol violations.
- Uncontrolled arterial hypertension

Intra-arterial and combined (IV+IA) thrombolysis

Intra-arterial thrombolytic treatment of proximal MCA occlusion using pro-urokinase within 6 hours of the event was associated with a significantly better outcome in the PROACT II trial (Prolysis in Acute Cerebral Thromboembolism Trial). (81) Additional randomized clinical trials with pro-urokinase (PROACT I) or urokinase (MELT) and a meta-analysis of PROACT I, PROACT II and MELT studies indicate a benefit of intra-arterial thrombolytic therapy in patients with proximal MCA occlusions. Pro-urokinase is not available and intra-arterial thrombolytic therapy with rtPA is not substantiated by clinical trials, though observational data and non-randomized comparisons are available. (82, 83)

A randomized trial (IMS3) comparing standard intravenous rtPA therapy with a combined intravenous low dose (0.6 mg/kg) and intra-arterial strategy is in progress. (84, 85) In 1999, the Emergency Management of Stroke Study was completed. The bridging study consisting of low dose intravenous

rtPA (0.6 mg/kg) followed by an intra-arterial dose of 20 mg was compared with a group receiving only intra-arterial therapy. Patients under bridging therapy showed higher recanalization rates but failed to show associated functional improvement, evidencing a statistical trend towards higher hemorrhagic complications and death. (86)

Intra-arterial treatment of acute basilar artery occlusion with urokinase or rtPA has been available for more than 20 years, but has not been tested in a sufficiently ample randomized clinical trial, although encouraging results have been obtained in observational studies related to higher recanalization rates, but without significant clinical improvement. (87)

Table 5. BP management

- BP levels should be lower than 185/110 mm Hg before infusion.
- If BP levels are > 185/110 mm Hg in two separate measurements at 5 to 10-minute intervals, one or two boluses of labetalol 10 to 20 mg IV should be administered at 10 to 20 minute separation intervals.
- If BP does not decline with these measures, the thrombolytic agent should not be administered.
- If BP elevation occurs during infusion: labetalol 10 to 20 mg IV repeated every 2 to 5 minutes, up to a maximum dose of 300 mg, or labetalol infusion at 2 to 8 mg/minute should be administered.
- If nitroprusside is used, the dose is 0.25 to 10 µg/kg/min.

Intra-arterial recanalization devices

The MERCI (Mechanical Embolus Removal in Cerebral Embolism) trial evaluated a device that removes the thrombus from an intracranial artery. Recanalization was achieved in 48% (68/141) of the patients in whom the device was deployed within 8 hours of the onset of symptoms. Patient assessment at 90 days showed a score < 2 in the modified Rankin scale in 27.7% of the cases and a mortality rate of 43.5%. This study evidenced lower recanalization than that obtained with intra-arterial thrombolysis in the PROACT II study. (88, 89) The Multi-MERCI trial evaluated state-of-the-art devices, including patients whose arteries were not recanalized after intravenous treatment. Favorable clinical outcome (36%), mortality rate (34%), and arterial recanalization rates were improved compared with the MERCI trial. There are no randomized clinical trials that confirm the clinical efficacy of recanalization devices. (90, 91)

Antiplatelet therapy

The results of two large, open-label, interventional studies indicate that aspirin is safe and effective when started within the first 48 hours after the ischemic event. In absolute terms, 13 more patients were alive and independent for every 1000 treated patients. Furthermore, treatment increased the odds of making a complete recovery from stroke (OR 1.06; 95% CI 1.01-1.11): 10 more patients made a complete recovery for every 1000 treated patients. Antiplatelet therapy was associated with a discreet increase of symptomatic intracranial hemorrhages; 2 for every 1000 treated patients. However, this was offset by the reduction of 7 recurrent ischemic stroke cases and one pulmonary embolism for every 1000 treated patients. (92-94)

The assessment of clopidogrel and combined aspirin-dipyridamole during acute stroke was only reported in 1360 patients who were treated within the first 72 hours, as part of a subanalysis of the PROFESS trial designed for secondary prevention. Treatment with combined aspirin-dipyridamole vs clopidogrel did not differ in terms of effects on functional outcome, recurrence, and death. (95)

Early anticoagulation

Subcutaneous unfractionated heparin (UFH) at low or moderate doses, nadroparin, certoparin, tinzaparin, dalteparin, and intravenous danaparoid have failed to show an overall anticoagulation benefit when initiated within 24 to 48 hours after the onset of ischemic stroke. Improvement in clinical outcome and reduction in ischemic recurrence rates were counterbalanced by an increased number of hemorrhagic complications. In a meta-analysis of 22 trials, anticoagulant therapy was associated with approximately 9 less recurrent ischemic events per 1000 treated patients (OR 0.76; 95% CI 0.65-0.88), and with approximately 9 more symptomatic intracranial hemorrhages per

1000 treated patients (OR 2.52; 95% CI 1.92-3.30). However, the quality of the trials varied considerably. The anticoagulants tested were unfractionated heparin, low molecular weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. (96, 97)

Few clinical trials have assessed the risk-benefit ratio of early administration of UFH in acute infarction. In one study, patients with nonlacunar ischemic stroke anticoagulated within 3 hours of the event had more self-independence (38.9% vs. 28.6%; $p = 0.025$), fewer deaths (16.8% vs. 21.9%; $p = 0.189$), and more symptomatic intracranial hemorrhages (6.2% vs. 1.4%; $p = 0.008$). In the RAPID (Rapid Anticoagulation Prevents Ischemic Damage) trial, patients treated with UFH had fewer early recurrent ischemic strokes and a similar incidence of serious hemorrhagic events, compared with those receiving aspirin. (98) In the UFH group, ischemic or hemorrhagic worsening was associated with inadequate plasma levels of heparin. Randomized clinical trials have not shown a net benefit of heparin for any ischemic stroke subtype. (99, 100)

Despite lack of evidence, some experts recommend full-dose heparin therapy in selected patients, such as those with cardiac sources of embolism with high risk of re-embolism, arterial dissection, or high-grade arterial stenosis prior to surgery. Contraindications for heparin treatment include large infarcts (e.g. more than 50% of MCA territory), uncontrolled arterial hypertension, and microvascular disease in the brain with microbleeds. (101,102)

Neuroprotection

No neuroprotection strategy has shown improved outcome on its predefined primary endpoint.

Recommendations

- Intravenous rtPA is recommended with an extended time window of up to 4.5 hours and not more than 3 hours in patients > 80 years of age with NINDS and ECASS III inclusion and exclusion criteria (Class I, Level of Evidence A and Class I, Level of Evidence B).
- Aspirin (100-325 mg) should be administered within the first 24 hours in patients who are not treated with rtPA, and after this period, in those who received thrombolytic therapy (Class I, Level of Evidence A and Class III, Level of Evidence A).
- In case of contraindication for systemic thrombolysis, the use of intra-arterial thrombolysis is limited to patients up to 6 hours after onset of symptoms in specialized centers (Class II, Level of Evidence B).
- The use of neuroprotection is not recommended (Class III, Level of Evidence A).
- The use of heparin is not recommended for the treatment of ischemic stroke (Class III, Level of Evidence A).
- The use of mechanical devices is not approved for

the treatment of ischemic stroke (Class II, Level of Evidence B).

7. SURGICAL TREATMENT OF ISCHEMIC STROKE

Decompressive surgery Malignant MCA infarction

The pooled analysis of 93 patients included in the DECIMAL (Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarcts), DESTINY (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery), and HAMLET (Hemicraniectomy after Middle Cerebral Artery Infarction with Life-Threatening Edema Trial) trials showed that, compared with the control group, the decompressive surgery group had more patients with a score ≤ 4 or ≤ 3 in the Rankin scale, and reduced mortality (NNTs 2, 4, and 2, respectively) one year after the event. Inclusion criteria for this combined analysis were: age 18-60 years, NIHSS > 15 , decrease in the level of consciousness scoring 1 or more on the item 1a of the NIHSS, 50% or more infarct signs of the MCA territory in the CT scan or $> 145 \text{ cm}^3$ in diffusion sequences and < 48 hours of infarction evolution. (103, 104)

Cerebellar infarction

Ventriculostomy and decompressive surgery are considered treatments of choice for space-occupying cerebellar infarctions, although randomized clinical trials are lacking. As 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 patients who are comatose before surgery. (105, 106)

Recommendations

- Surgery in malignant infarctions is recommended, prior to signs of herniation, in young patients with infarctions in non-dominant hemisphere (Class II, Level of Evidence C).

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9. APPENDIX 1

Definition of Class and Level of Evidence used by the American Heart Association

Class I: condition for which there is evidence and/

or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Class II: condition for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: the weight of evidence or opinion is in favor of a procedure or treatment.

Class IIb: usefulness/efficacy is less well established by evidence or opinion.

Class III: condition for which there is evidence and/or general agreement that a given procedure or treatment is not useful/effective and in some cases may be harmful.

Level of Evidence A: data derived from multiple randomized clinical trials.

Level of Evidence B: data derived from a single randomized study or from non-randomized studies.

Level of Evidence C: Expert opinions or case studies.

10. APPENDIX 2

Recommendations	Population needs	Organization and operation of the health care system	Costs	Availability of resources	Beliefs and values of the target population	Equity	Applicability
All stroke patients should be treated in a Stroke Unit or at the EMS by trained staff (Class I, Level A).							7
Health care systems should ensure stroke patients have access to high technology medical and surgical care when required (Class I, Level B).		X	X	X			6
The development of clinical networks, including telemedicine, is promoted to expand the access to high-technology, specialized medical care (Class II, Level B).		X	X				6
Employ screening scales in the prehospital stage to identify patients with possible diagnosis of stroke (Class II, Level B).							7
Apply the NIHSS scale to quantify the neurological deficit and later patient follow-up (Class II, Level A).							7
In patients with suspected TIA or stroke, urgent CT scan should be performed (Class I, Level A), or alternatively MRI (Class II, Level A) .			X	X			6

Recommendations	Population needs	Organization and operation of the health care system	Costs	Availability of resources	Beliefs and values of the target population	Equity	Applicability
If MRI is used, include diffusion-weighted imaging, apparent diffusion coefficient (ADC), gradient echo sequences, and FLAIR (Class II, Level A).							7
In patients with TIA and ischemic stroke, immediate diagnostic vascular work-up is necessary (ultrasound, CT-angiography, or MR-angiography) (Class I, Level A).							7
Based on Good Clinical Practice Guidelines (GCP), neurological status, heart rate, blood pressure and oxygen saturation should be monitored in patients with ischemic stroke.							7
Oxygen should be administered if oxygen saturation is < 92% (GCP).							7
Maintain a neutral fluid balance and correct hydro-electrolyte imbalance in patients with ischemic stroke (GCP).							7
Normal saline (0.9%) should be used as fluid replacement therapy during the first 24 hours after the onset of ischemic stroke (GCP).							7
As a general rule, routine blood pressure (BP) should be lowered during ischemic stroke (GCP).							7
Elevated BP should be lowered in patients with extremely high blood pressure levels on repeated measurements, and with clinical evidences of acute myocardial infarction, severe cardiac failure, aortic dissection, pregnancy, renal failure, or hypertensive encephalopathy (> 220/120 mm Hg) (GCP).							7
Blood volume expanders should be used to treat hypotension secondary to hypovolemia or associated with neurological deficit during acute ischemic stroke (GCP).							7
Monitor serum glucose levels (GCP).							7
Treat serum glucose levels > 180 mg/dl with insulin (Class II, Level B).							7

Recommendations	Population needs	Organization and operation of the health care system	Costs	Availability of resources	Beliefs and values of the target population	Equity	Applicability
Correct hypoglycemia (< 50 mg/dl) with intravenous dextrose or 10-20% glucose infusion (Class II, Level B).							7
Lower temperature > 37.5 °C with paracetamol or physical measures (GCP).							7
Search for concurrent infection in case of hyperthermia (GCP).							7
Prescribe low-dose heparin to prevent deep vein thrombosis and pulmonary thromboembolism (Class II, Level A).							7
Regular prophylactic administration of anticonvulsants is not recommended. It should only be indicated in patients with a history of seizures or ischemia with cortical hemorrhagic transformation (Class II, Level B)							7
Intravenous rtPA with an extended time window of up to 4.5 hours, and not more than 3 hours in patients > 80 years with NINDS and ECASS III inclusion and exclusion criteria is recommended (Class I, Level A).			X	X			6
Aspirin should be indicated within the first 24 hours in patients who are not treated with rtPA, and after this period, in those who received thrombolytic therapy (Class I, Level A)							7
In case of contraindication for systemic thrombolysis, the use of intra-arterial thrombolysis is limited to patients up to 6 hours after onset of symptoms in specialized centers (Class II, Level B).		X	X	X			5
The use of neuroprotection is not recommended (Class I, Level A).							7
The use of heparin is not recommended for the treatment of ischemic stroke (Class I, Level A).							7
The use of mechanical devices is not approved for the treatment of ischemic stroke (Class II, Level B).		X	X	X			5

Recommendations	Population needs	Organization and operation of the health care system	Costs	Availability of resources	Beliefs and values of the target population	Equity	Applicability
Surgery in malignant infarctions, prior to signs of herniation, is recommended in young patients with non-dominant hemisphere infarction (Class II, Level C).				X			6

NOTE: Final applicability score goes from 0 (not applicable) to 7 (maximum applicability). Dimensions with compromised applicability are marked with "X". (Based on the tool for Evaluation of Applicability of Clinical Practice Guidelines by professional users from the National Academy of Medicine in Argentina.)