

Guidelines for acute ischemic stroke treatment – Part I

Diretrizes para tratamento do acidente vascular isquêmico – Parte I

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These guidelines are a result of several meetings from the Brazilian Stroke Society (Sociedade Brasileira de Doenças Cerebrovasculares – SBDCV, website www.sbdcv.org.br), which represents the Scientific Department in cerebrovascular diseases of the Brazilian Academy of Neurology, responsible for technical opinions and educational projects related to cerebrovascular diseases. Members from SBDCV participated in web-based discussion forum with pre-defined themes, followed by a formal onsite meeting in which controversies and final position statements were discussed. Finally, a writing group was created to revise and translate the final document, which was approved by all members of the SBDCV. The final text aims to guide specialists and non-specialists in stroke care in managing patients with acute ischemic stroke. The hemorrhagic stroke guideline has been previously published by the same group¹. In the final recommendations, Oxford classification for evidence level and recommendation grade was used:

EVIDENCE LEVELS

1. Randomized controlled clinical trial (RCT) or systematic review (SR) of RCT with clinical endpoints.
2. RCT or SR of lower quality: with substitute, validated endpoints; with subgroup analysis or with *a posteriori* hypotheses; with clinical endpoints, but with methodological flaws.

3. RCT with substitute, non-validated endpoints case-control studies.
4. Study with clinical endpoint, but with a higher potential bias (as in experiment without comparison group and other observational studies).
5. Representative forum or expert opinion without above-mentioned evidence.

RECOMMENDATION GRADES

- A Systematic review (homogeneous) of RCT; or single RCT with narrow confidence interval; or therapeutic results of “all or nothing” type.
- B Systematic review (homogeneous) of cohort studies; or cohort study and RCT of lower quality; or outcomes research or ecological study; or systematic review (homogeneous) of case-control studies; or case-control study.
- C Case reports (including cohort or case-control study of lower quality).
- D Expert opinion without critical evaluation, based on physiological or animal studies.

In this first part of the guidelines, specific topics included were: epidemiology, stroke as a medical emergency, education, pre-hospital management, emergency management, neuroimaging and laboratory evaluation. A translated version of these guidelines in Portuguese is available in the Society's webpage (www.sbdcv.org.br).

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EPIDEMIOLOGICAL ASPECTS

Among the 58 million deaths per year worldwide, 5.7 million were caused by stroke. Therefore, stroke was the second most common cause of death, responsible for 10% of all deaths in world². However, the global distribution is heterogeneous, as 85% of deaths occurred among developing countries and one-third affected economically active individuals^{2,3}. This impact is expected to increase in the next decades, as projected by a 300% increase in the elderly population of developing countries in the next 30 years, specially in Latin America and Asia⁴.

In Brazil, stroke was responsible, in 2005, for 10% of all deaths (90,006 deaths) and for 10% of all public hospital admissions^{4,5}. In that year, Brazil spent 2,7 billion dollars in health care on cardiac diseases, stroke and diabetes mellitus^{4,5}.

In Latin America, stroke incidence rates adjusted for age vary between 35 and 183 per 100,000⁶, and, in Brazil, vary between 137 and 168 per 100,000 inhabitants⁷⁻⁹. In two recent studies of stroke-related mortality, a steady drop in mortality rates were observed in the last two decades^{10,11}. Although the reasons for this drop are unknown, classically mortality rates are directly related to changes in incidence or lethality rates¹¹. Incidence rates are influenced by socio-economical conditions and quality of primary prevention, while lethality is dependent on disease severity of the sample and quality of hospital care¹¹. Any combination of these factors may have improved in Brazil during this time period.

STROKE: A MEDICAL EMERGENCY

The concept of stroke as a medical emergency is still not well established in Brazil. In a recent study performed in four Brazilian cities, with 814 individuals, 28 different names were given for stroke¹². Only 35% knew that “192” was the appropriate emergency number in Brazil, 22% did not recognize any stroke warning sign, and only 51% would call for emergency rescue if a family member had symptoms of stroke.

Studies on recognition and activation of emergency services performed in developed countries have systematically concluded that interventions are necessary to increase the number of patients eligible for acute stroke treatment, such as educational campaigns targeting the immediate recognition of warning signs, triggering a proactive attitude towards rescuing the stroke victim.

Thus, the delay in reaching acute stroke care can be identified as one among many different factors that influence lethality. Other factors include: early identification of warning signs by the population, recall and correct use of the national emergency number “192”, emergency rescue triage and prioritization in transportation, hospital diagnosis,

communication between health professionals and early access to neuroimaging.

The causes of delay in pre-hospital care include the lack of knowledge of stroke warning signs, denial of disease state and the hope of spontaneous resolution of symptoms. Educational initiatives should target patients at risk, as well as their family members. Considering that approximately 45-48% of patients are referred by a general clinician, educational campaigns should also be directed towards the medical community, emphasizing the importance of emergency treatment¹³.

Eight non-randomized studies evaluated the impact of educational measures on health care of the stroke victim; they demonstrated that thrombolysis rate increased after the educational campaign, but only during six months. This shows that an educational intervention requires periodic recycling in order to maintain a positive result¹⁴⁻²¹.

Recommendations

Periodical educational programs to increase stroke awareness in the general population are recommended (level of evidence: 1, recommendation grade: B).

Periodical educational programs to increase stroke awareness among medical professionals, other health professionals and emergency services are recommended (level of evidence: 1, recommendation grade: B).

PRE-HOSPITAL CARE AND TRANSPORTATION

Stroke is a medical and eventually surgical emergency. After time-dependent therapies have demonstrated to be successful; acute stroke management is tightly linked to this concept of emergency care. However, only a minority of patients arrive at emergency rooms on time to benefit from reperfusion therapies for the region affected by ischemia or for control of intracerebral hemorrhage²²⁻²³. This delay is due to a series of factors, including lack of knowledge of stroke warning signs to underutilization of specialized rescue services, as the Serviço de Atendimento Móvel de Urgência – SAMU (Mobile Emergency Service) in Brazil^{12,20,24-26}. Many studies have demonstrated that utilization of private vehicles or previous contact with a primary care physician increase the time between stroke onset and hospital admission, often delaying or contraindicating reperfusion therapy²⁷⁻³¹. However, SAMU does not exist in all Brazilian cities and in many ones it suffers from lack of equipments, human resources, educational training programs, besides the lack of a structured protocol for stroke management. Many cities also lack reference hospitals for acute stroke treatment. A multidisciplinary approach, using written protocols associated with health professional training and recycling, involving every link in a chain of pre-hospital care, is an important differential in acute stroke treatment³²⁻³⁵.

Aiming for a rapid sequence of recognition, emergency service activation and stroke victim rescue, transportation and treatment to become standard of care in Brazil, we recommend:

1. To initiate educational campaigns targeted toward the population, aiming at recognition of stroke warning signs and immediate activation of emergency medical services (level of evidence: 1, recommendation grade: B)^{12,20,24-26,32,36}.
2. To encourage the immediate use of SAMU (telephone number 192) or other pre-hospital emergency services in case of an acute stroke identification. These possibilities of access should be highly publicized and known by the general population. Due to eventual communication difficulties by the patient, in cases of telephone contact, the central station should have telephone-localization capabilities (level of evidence: 1, recommendation grade: B)^{12,27,28,30,32}.
3. The SAMU and other pre-hospital mobile systems should give maximum priority to acute stroke victims, and their professionals should be prepared to recognize, perform a basic differential diagnosis and initiate management of acute stroke using specific scales and protocols. Once stabilized, transportation should be prioritized to a hospital with the best relationship between distance/technical quality, notifying the hospital previously by radio or telephone (level of evidence: 1, recommendation grade: B)^{32,35,37,38}.
4. To perform training and continuous education for SAMU and other pre-hospital mobile system professionals (telephone service professional, MD, ambulance professionals), so that they may quickly recognize and trigger decisions on initial treatment, transportation and final destination when a stroke victim is identified (level of evidence: 1, recommendation grade: B)^{20,32,33}.
5. To adopt, in all pre-hospital transportation: monitorization of oxygen saturation, and in all who have saturation below 95% to apply oxygen supplementation; clinical evaluation of hydration and, in case of dehydration, to apply intravenous hydration with 0.9% normal saline; finger stick testing for blood glucose, and to dispense glucose-containing fluids only in case of detected hypoglycemia (level of evidence: 1, recommendation grade: B)³⁹⁻⁴²; and not to treat systemic hypertension routinely (level of evidence: 1, recommendation grade: C)³².
6. To adopt, in all pre-hospital transportation, the systematic use of evaluation and pre-hospital triage scales, such as the Cincinnati and Los Angeles scales, to identify stroke patients, specially those who are candidates for reperfusion therapy (level of evidence: 1, recommendation grade: C)^{34,35}.

STROKE IN THE EMERGENCY DEPARTMENT

The treatment of stroke patients in the emergency must begin with the evaluation of vital functions (ABC) and the

establishment of basic support, as it is not possible to safely proceed in any diagnostic or therapeutic decision without them.

Stroke is the main differential diagnosis in patients with neurological deficits of sudden onset. In such cases, a written and multi-professional protocol allows fast diagnostic and therapeutic settling. Clinical and neurological evaluation scales assist in the standardization of the monitoring process and prognostic estimate of the cases. The treatment of stroke patients accompanied by a neurologist seems to improve the diagnostic and prognostic accuracy for these patients⁴³⁻⁵³.

It is fundamental to consider the possibility of differential diagnoses. In most cases, this is possible with information of the patient's clinical history, supported by complementary exams (neuroimaging and laboratory tests)^{54,55}.

Stroke patients may present, as a cause or consequence, multiple organ dysfunctions, which justifies carrying out further tests. Some changes of cardiac function, particularly arrhythmias and acute myocardial infarction, are common after a stroke⁵⁶⁻⁶².

There is no evidence in favor of oxygen supplementation for all patients in the acute phase of stroke. It is assumed, however, that maintaining a good oxygenation is important, especially in the penumbra region, the main therapeutic target in ischemic stroke at this stage. Altered consciousness, seizure, aspiration pneumonia, heart failure and pulmonary thromboembolism are possible complications that require special ventilatory care, although the necessity of orotracheal intubation determines, frequently, a poor prognosis^{39,63,64}.

Dehydration in stroke patients is usually associated with a worse prognosis. Although there is no evidence of the intravenous fluid supply impact during the acute phase of stroke, it is accepted that the maintenance of adequate hydration favors homeostasis. It is observed that specialized services for the treatment of stroke (stroke units) make use of a more aggressive intravenous hydration. Hypotonic fluids, however, can bring harm, as they elevate the risk of cerebral edema and intracranial hypertension, especially in extensive infarcts^{65,66}.

Hyperglycemia occurs in more than half of the patients in the acute phase of stroke, even the ones with no history of diabetes mellitus, and it is associated with increased morbidity and mortality, regardless of age, the mechanism of ischemic stroke or the extent of the ischemic injury. Glucose

Table. Recommendations of ideal times in the treatment of stroke in Emergency.

From admission to medical evaluation	10 minutes
From admission to cranial CT (end)	25 minutes
From admission to cranial CT (interpretation)	45 minutes
From admission to infusion of rt-PA	60 minutes
Availability of neurologist	15 minutes
Availability of neurosurgeon	2 hours
From admission to monitored bed	3 hours

levels above 140 mg/dL are associated with worse outcomes in thrombolytic treatment and worse functional prognosis in 90 days. However, it is not clear whether normalizing glucose levels have a positive impact on prognosis, as well as the best way to correct hyperglycemia, which remains controversial. On the other hand, hypoglycemia can cause neurological dysfunction or tissue damage, representing a differential diagnosis of stroke^{40,67-75}.

Hypertension is commonly observed in acute ischemic stroke. Reasons for this phenomenon include physiological compensation due to brain ischemia and reactive increase in mean arterial pressure secondary to progressive elevation of intracranial pressure. Some studies demonstrate neurological worsening associated with reduced blood pressure, especially on the first day. However, the recent CHHIPS study did not demonstrate neurological worsening in the actively treated group (after a 72-hour evolution), but the group with antihypertensive treatment started immediately presented lower mortality at three months. Other issues include the possibility of different effects of blood pressure reduction on the ischemic brain tissue in normotensive and hypertensive individuals, and the influence on intracranial pressure, determined by antihypertensive drugs, such as sodium nitropruside and hydralazine, which present an intracranial vasodilator property. The answers to what would be the optimal values of blood pressure and what would be the indications and best forms of control during this period remain controversial. The tendency is to avoid aggressive interventions in acute stroke⁷⁶⁻⁸⁰.

Hypotension is rare in acute stroke patients and is usually associated with acute myocardial infarction, congestive heart failure, hypovolemia and sepsis. In a further analysis from the International Stroke Trial (IST), levels of systolic blood pressure ≤ 140 mmHg were associated with worse prognosis, which was proportionally greater for every 10 mmHg decrease in systolic blood pressure⁸¹.

Clinical and experimental observational studies show the association between hyperthermia and a worse stroke prognosis. Possible reasons for this include increased metabolic demand in a context of brain ischemia, excitotoxicity and increased local inflammatory response⁸²⁻⁸⁵.

Recommendations

1. The treatment directed towards the type of stroke diagnosed (ischemic stroke, intraparenchymal hemorrhage or subarachnoid hemorrhage) must be initiated within 60 minutes of admission to the hospital service, ideally observing the times in Table. (level of evidence: 5; recommendation grade: D)
2. Development and application of multi-professional, integrated written protocols, for the treatment of any suspected stroke cases. (level of evidence: 3B; recommendation grade: B)
3. The treatment of a stroke patient should be guided by a neurologist. (level of evidence: 2B, recommendation grade: B)
4. Perform laboratory tests for exclusion of differential diagnoses and therapeutic decision aid. (level of evidence: 5, recommendation grade: D)
5. Perform neuroimaging tests to guide therapy in acute phase of stroke. (CT – level of evidence: 1, recommendation grade: A; or MRI – level of evidence: 2B, recommendation grade: B)
6. Non-invasive cardiovascular monitoring (level of evidence: 5, recommendation grade: D)
7. Blood oxygen saturation must be evaluated in patients with acute stroke, if possible, with pulse oximetry. (level of evidence: 5, recommendation grade: D)
8. Oxygen supplementation should only be performed, if necessary, to maintain oxygen saturation at levels equal to or above 95% (level of evidence: 2B, recommendation grade: B)
9. The indication for ventilatory support and airway protection should be carefully evaluated, especially in patients with lowered level of consciousness and neurological symptoms suggestive of brainstem ischemic stroke. (level of evidence 5, recommendation grade: D)
10. The patient with acute stroke should be adequately hydrated with isotonic saline solution (e.g. 0.9% saline). The volume administered intravenously (around 100 mL/hour) should be considered individually, based on the baseline hydration and possible comorbidities that limit water supply. (level of evidence: 4, recommendation grade: C)
11. Evaluate the possible diagnosis of diabetes mellitus in patients with hyperglycemia in acute stroke, even if previously healthy, through examination of glycosylated hemoglobin. (level of evidence: 4, recommendation grade: C)
12. Prevent and treat additional causes of hyperglycemia (e.g. corticosteroids and infection). (level of evidence: 5; recommendation grade: D)
13. Use insulin to correct hyperglycemia, aiming to keep blood glucose between 80 and 140 mg/dL. (level of evidence: 5; recommendation grade: D)
14. Promptly correct hypoglycemia (blood glucose below 70 mg/dL). (level of evidence: 5; recommendation grade: D)
15. Do not reduce blood pressure in acute ischemic stroke, except when levels are extremely high (SBP>220 mmHg or DBP>120 mmHg). In these cases, reduction must not exceed 15% of the initial blood pressure values in the first 24 hours. (level of evidence: 5, recommendation grade: D)
16. Use antihypertensive medication in patients with indication for thrombolytic treatment, but with blood pressure $\geq 185 \times 110$ mmHg before the start of the treatment. (level of evidence 1; recommendation grade: A)
17. Utilize antihypertensive medication in acute stroke patients which, even with moderate elevations of blood

pressure, present other medical indications for urgent treatment (hypertensive emergencies), such as heart failure, aortic dissection, acute myocardial infarct and acute renal failure. (level of evidence: 5; recommendation grade: D)

18. Do not abruptly reduce blood pressure in acute stroke. For this reason, the use of nifedipine is contraindicated. (level of evidence: 4; recommendation grade: C)
19. Blood pressure must be kept above a mean arterial pressure of 90 mmHg. This must be done through the administration of isotonic fluids, as saline solution, and, when necessary, volume expanders and vasoactive drugs. Some drugs are used for this purpose, such as norepinephrine, dopamine and phenylephrine. Due to the absence of inotropic and chronotropic effect (β -adrenergic action), thereby reducing the risk of heart complications, phenylephrine may be a preferable option in patients with prior heart disease. (level of evidence: 5; recommendation grade: D)
20. Keep axillary temperature below 37.5°C. If necessary, antipyretic medications should be used, as acetaminophen and dipyrone. (level of evidence 5, recommendation grade: D)
21. In cases of hyperthermia, investigate infectious causes. Fever of central origin should always be an exclusion diagnosis. (level of evidence 5; recommendation grade: D)

IMAGING IN ACUTE STROKE

Head CT without contrast is essential in the emergency assessment of patients with acute ischemic stroke. It identifies 90-95% of subarachnoid hemorrhages and almost 100% of intraparenchymal hemorrhages, and helps to rule out non-vascular causes of neurological symptoms^{86,87}.

In patients with involvement of the middle cerebral artery (MCA), early signs of ischemia are present in approximately 60% of the cases with only two hours from symptom onset⁸⁸, and in 82% of the cases within six hours⁸⁹, and are associated with worse prognosis⁹⁰. The presence of these signs affecting a large area of brain tissue is also associated with greater risk of hemorrhagic transformation after the use of thrombolytic medication, especially when the territory is larger than one-third of the MCA⁹⁰. Specific training is needed to recognize these signs and define the true extent of the affected area in the CT⁹¹⁻⁹⁴. The use of ASPECT score for the evaluation of early ischemic alterations objectively quantifies the affected territory, can improve detection of the affected area and provide information about prognosis, but is not validated to include or exclude patients from thrombolysis^{32,95}. The only early sign used as an exclusion criterion for the treatment is hypodensity in more than one-third of MCA territory.

Although head CT has relatively low sensitivity in detecting small acute infarcts, especially in the posterior fossa, it is still the first-line test in most centers using thrombolytic

treatment. Head CT for acute phase evaluation is sufficient, fast, available in most emergencies and may exclude the possibility of intracranial hemorrhage, possibly providing prognostic information (early signs)^{55,86}. Since time is crucial, patients with acute stroke should be given priority over other patients for brain imaging. A CT scan performed immediately is the most cost-effective strategy for the imaging evaluation in patients with acute stroke⁹⁶. In patients with indication for thrombolytic therapy, CT should be performed within 25 minutes after patient admission, and interpretation must be obtained in the next 20 minutes⁹⁶.

Some centers prefer using cranial MRI, with diffusion-weighted imaging (DWI) technique, in the routine investigation of acute stroke. It has greater sensitivity to identify the ischemic region (as early as 35 minutes of symptom onset), and image acquisition takes only a few seconds⁹⁷. However, not all MRI systems are capable of performing DWI. MRI is particularly useful in posterior circulation strokes, lacunar infarctions, small cortical infarcts and, above all, in unusual images when there are doubts as to the diagnosis of stroke. Gradient echo-sequences allow exclusion of hemorrhage with sensitivity and specificity of 100%⁹⁸. Thrombolytic initiation must not be delayed to carry out MRI^{99,100}.

The difference between the volume of DWI signal change (corresponds, in most cases, to the core of brain tissue already infarcted)¹⁰¹ and the perfusion image (brain tissue with critical hypoperfusion) is called *mismatch* (corresponds to the penumbra, volume of ischemic potentially reversible brain tissue)¹⁰². This feature may be used in thrombolysis decisions based on the persistency of ischemic penumbra in individuals beyond the approved therapeutic window¹⁰³ or in cases of uncertain time of symptom onset, despite no evidence of a major response to thrombolysis up to nine hours¹⁰⁴. Recently, dynamic perfusion imaging in CT has been used as an alternative to this method^{105,106}.

Performing emergency angiography or magnetic resonance angiography of intra and extracranial vessels to detect occlusions or stenosis of large vessels in the acute phase of stroke may be used in centers that provide structure for intra-arterial recanalization treatment^{107,108}.

Transcranial doppler (TCD) is useful for the diagnosis of occlusions of major brain arteries and may be used to monitor the effects of thrombolytic therapy in the acute phase, besides aiding in prognosis determination¹⁰⁹⁻¹¹¹. However, between 7 and 20% of patients with acute stroke do not have an adequate acoustic window^{112,113}.

Recommendations

1. For patients with acute stroke, an urgent noncontrast head CT is recommended (level of evidence: 1A, recommendation grade: A) or, alternatively, cranial MRI with the inclusion of diffusion and gradient echo sequences. (level of evidence: 1B, recommendation grade: A)

2. Brain imaging must be interpreted by a physician with cranial CT or MRI evaluation training. (level of evidence: 5, recommendation grade: D)
3. The use of multimodal neuroimaging can be useful for patient selection for thrombolytic therapy in patients with onset of symptoms with an indefinite duration or beyond 4 hours and 30 minutes. (level of evidence: 3, recommendation grade: C).

LABORATORIAL INVESTIGATION

Inflammation markers in stroke

All phases of atherothrombosis are characterized by a vascular inflammatory process. However, there are no specific studies proving the validity of these markers in acute stroke. The predictive value of complications (progression of thrombosis, new arterio-arterial emboli) or of indication of any intervention in the acute phase based in biomarkers is still not well-established¹¹⁴. While systematic reviews of the role of blood biomarkers in the diagnosis of ischemic stroke show that we still cannot recommend these tests in clinical practice, it is highly desirable that new studies be performed so that a faster diagnosis of ischemic stroke may be possible, even before reaching the hospital, through biological markers of cerebral ischemia or inflammation¹¹⁵.

Chest x-ray

Performed routinely even without evidence of cardiac or pulmonary disease, chest x-rays have been subject of various studies, showing that it may change management in 3.8% of the cases. Although it is a small percentage, it is not negligible¹¹⁶.

Glucose

In relation to glucose levels, importance resides in defining if the clinical situation is a stroke or hypoglycemia, which can mimic it. Hyperglycemic values are also important, as they can indicate unfavorable prognosis.

Exams in the subacute phase to define etiology and act upon risk factors

Stroke patients are at increased risk of recurrence, and our action is needed to reduce this risk with secondary prevention measures. With this objective, we must recognize individual risk factors. In relation to the lipid profile, it is necessary to mention studies from Amarenco, which showed

reduction of stroke risk, resulting from a 50% or more decrease of LDL-C levels. In this context, there was a 31% reduction in stroke risk, 33% reduction of ischemic stroke, with no statistically significant increase in hemorrhage stroke incidence, as well as 37% decrease in major coronary events¹¹⁷.

Laboratory exams in emergency must be quickly available and cannot be the reason to delay the use of thrombolytics (expert consensus).

Thus, it is well established the requirement, on admission, of exams, such as complete blood count, blood glucose and glycosylated hemoglobin (in cases of hyperglycemia), creatinine, urea, electrolytes, arterial blood gas analysis and coagulation, as well as electrocardiogram and cardiac enzymes, due to the common comorbidity of acute myocardial infarction. (level of evidence: 5; recommendation grade: D)

Exams to be requested in the sub-acute phase: lipid profile, serology for Chagas' disease and syphilis, and, in young patients, in addition to the ones already mentioned, evaluation of autoimmune diseases, arteritis, homocysteine levels, AVM research, coagulopathy and genetic profile for thrombophilia. (level of evidence: 5, recommendation grade: D)

Examination of CSF is only recommended when there is strong evidence of subarachnoid hemorrhage with no blood evident on CT or when clinical investigation suggests infection as the cause of the deficit.

EEG is indicated when seizure is the possible cause for the deficit or when it is a complication of the stroke. It may be a differential diagnosis of stroke and may change treatment indication¹¹⁸.

There is indication of ECG, transthoracic echocardiography, Holter monitoring and cardiac enzymes for cases of cardiac arrhythmias with suspected embolic stroke, either by atrial fibrillation, acute myocardial infarction with ventricular dysfunction, valvular failure or in dilated heart disease, such as in Chagas' disease¹¹⁹.

In young patients, the execution of transesophageal echocardiography is preferable due to the incidence of patent foramen ovale. Other exams will be performed as diagnostic hypotheses are raised and according to the necessity to evaluate treatment, as toxicologic exams, pregnancy tests and HIV serology.

In summary, laboratory exams will be divided in two phases of activity:

- In the emergency, for the diagnosis of stroke, for diagnosis of stroke type and for decision to apply treatment.
- At the hospital, to establish nosological diagnosis and apply secondary prevention measures.

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