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# ACUTE MANAGEMENT OF ISCHEMIC STROKE

## ABSTRACT:

**Introduction:** Ischemic stroke is the fourth cause of death and the first cause of long-term disability. Due to the seriousness of this topic, we have decided to focus on recommendations and controversies related to specific clinical and surgical matters, such as the acute management of ischemic stroke, and the controversies derived from the “combined management of the carotid disease and cardiac surgery”, and the “time of surgery in patients with symptomatic carotid atheromatous disease”.

**Aim:** To define the characteristics of the ischemic stroke, its diagnosis and treatment in the so-called “golden hour”; to unify criteria regarding the combined management of the carotid disease and the coronary disease as well as of patients with symptomatic carotid disease.

**Materials and method:** Review of the literature, reaffirming evidence-based medicine recommendations.

**Conclusions:** The detection, diagnostic testing and treatment of acute ischemic stroke in the first hour brings considerable benefits; with respect to patients with combined carotid and coronary disease, the endarterectomy would be prioritized over stenting, since the latter would cause greater delay for acute coronary revascularization due to the antiplatelet therapy implemented and increased risk of bleeding after cardiac surgery. Patients with symptomatic carotid stenosis  $\geq 70\%$  benefited more if they were operated on within the first 2 weeks after the ischemic stroke.

**Palabras Clave:** ischemic stroke, symptomatic carotid disease, cerebrovascular and cardiac disease.

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## INTRODUCTION

Ischemic stroke is the fourth cause of death and the first cause of long-term disability. Due to the seriousness of this topic, we have decided to focus on recommendations and controversies related to specific clinical and surgical matters, such as the management of acute care management of ischemic stroke, and the controversies derived from the “combined management of the carotid disease and cardiac surgery”, and the “time of surgery in patients with symptomatic carotid atheromatous disease”.

## RECOMMENDATIONS ON THE ACUTE MANAGEMENT OF ISCHEMIC STROKE

The proper initial assistance of these patients allows to reduce morbidity and mortality associated with this pathology. Two stages are clearly distinguished:

- 1) Pre-hospital stage.
- 2) Hospital stage during the first hour.

## PRE-HOSPITAL STAGE

### Early recognition of symptoms:

The sudden onset of neurological symptoms is the most important recognizing sign. However, about 20% of patients who are suspected of suffering from an ischemic stroke presents another pathology. The most frequent ones include metabolic encephalopathies for hypoglycemia, hyperglycemia or hyponatremia, subdural hematoma, central nervous system tumors, complicated migraine, post-convulsive condition (Todd's paralysis), brain abscess, meningoenzephalitis, exogenous intoxication and psychoactive drugs abuse. During the initial examination of these patients it is essential to ask for any history of vascular risk factors, seizures, trauma, chronic cephalaea, usual medication and toxic substances exposure. (1,2) The most frequent clinical characteristics of stroke are generally related to the sudden appearance of any of the following symptoms:

- Weakness or clumsiness in one side of the body.
  - Visual impairment of one eye or both.
  - Patient unusual acute cephalaea.
  - Vertigo or instability.
  - Dysarthria and language impairment.
  - Sensitivity alterations.
- 1) “While some observational studies show acceptable outcomes in combined surgery (6), others do not succeed in doing so”.

- 2) “In his *review*, Naylor details risk of death, stroke (30 days) and prevalence of death/perioperative stroke in patients with carotid lesions, between 50%-99%, and without prophylactic treatment, *from 3.8% - 3.8% and 3.8%, respectively.* (10)

The appearance of these symptoms should be a sign to call an emergency service and make an urgent transfer of the patient to hospital. During the pre-hospital stage, some tracking scales such as FAST and Cincinnati Scale may be used. It is important to record the time the symptoms first appeared to choose the proper subsequent treatment. (1)

## **HOSPITAL STAGE**

During the hospital stage, it is important to establish an adequate selection, allowing a quick detection of those patients who are in the therapeutic window for recanalization treatment.

Door-to-needle time should be less than 60 mins (golden hour), for which the implementation of guidelines or algorithms of treatment is advisable, as well as the establishment of priority codes for the performance of complementary studies. (3)

Since the hospital admission of the patient, several steps, shown in the attached algorithm, should be taken (*Figures 1 and 2*).

The measures to be taken are divided into two categories:

- 1) General management of ischemic stroke.
- 2) Specific acute management of ischemic stroke.

### **General management of ischemic stroke**

- ABC: to examine the adequate airway protection, oxygenation and hemodynamic stability.
- Vital signs monitoring: heart rate, blood pressure, pulse oximetry and temperature.
- 30° headboard – Neutral position. Nothing by mouth.
- Colocation of 2 high-flow peripheral venous catheters.
- PHP with normal saline. To keep the normal fluid balance.
- Oxygen by nasal cannula at 3 l per minute to ensure peripheral saturation higher than 95% (except as otherwise indicated by the clinical examination or the pulse oximetry, or an airway protection with orotracheal intubation may be necessary).
- To treat hyperthermia with physical means and paracetamol.
- To put urinary catheter and stomach tube for discharging as necessary.
- To control blood sugar and correct any deviation.
- NIHSS scale.

### **Complementary diagnostic studies**

- Lab tests: complete blood count, blood sugar, uremia, serum electrolytes, creatinine and baseline values of coagulation including INR. Cardiac enzymes in patients with changes in the electrocardiogram.

- Electrocardiogram.
- Chest x-ray.
- Imaging tests: brain CT, with angio-CT, whenever possible. A brain NMR may be performed as initial study, provided it does not delay treatment.

## **SPECIFIC TREATMENT MEASURES**

### **Blood pressure treatment**

In patients with ischemic stroke, blood pressure control should be conservative since blood hypotension could reduce brain blood flow and increase the ischemic area. It is considered adequate to reduce no more than 15% blood pressure values during the first 24 hours. The only clinical conditions that require more intensive management of blood pressure are: ischemic stroke in the context of aortic dissection, pregnancy, quickly progressive kidney failure, heart failure and signs of hypertensive encephalopathy. Patients undergoing rt-PA treatment should have a blood pressure lower than 185/110 mmHg during infusion and for 24 hours thereafter. The selected drug is labetalol by 10 and 20-mg intravenous bolus. If hypertension remains, continuous dripping may be initiated, controlling the heart rate. Patients with bradycardia requiring a more intensive blood pressure could begin with sodium Nitroprusside by continuous dripping. (4)

### **Antiplatelet drugs**

Patients who are not undergoing a thrombolytic treatment should begin the antiplatelet therapy within the first 24 hours. The only antiplatelet drug evaluated in two studies with almost 40,000 patients is aspirin. When given early, aspirin proved to reduce recurrence and mortality. The recommended initial dose ranges from 100 to 325 mg/day. (5)

### **Anticoagulants**

Anticoagulation was not effective as acute treatment of ischemic stroke. Bedridden patients after the vascular event or with moderate to severe motor deficit that prevents initial ambulation should receive heparin sodium or low molecular weight heparin for prophylaxis of deep venous thrombosis. (1)

### **Fibrinolytics**

Measures aimed at recanalization are based on the ischemic penumbra concept, which states that, by reducing the brain blood flow to critical levels, a few minutes later a main area is produced with irreversible ischemic changes. Such area is surrounded by a zone with electrocerebral silence but with undamaged cellular membranes. This zone, called ischemic penumbra, can restore its function if the flow is quickly restored. (1)

Intravenous rt-PA proved to be effective in doses of 0.9 mg/kg, with a maximum dose of 90 mg, when administered in a three-hour window based on the outcomes of the NINDS study. The meta-analyses of the intravenous rt-PA study showed that this benefit, although less significant, could be kept up to 4.5 hours, and this was confirmed by the ECASS III. In case of fibrinolysis, the symptomatic bleeding rate is 6.4 %, which seems to be associated with the severity of the neurological focus, the existence of extensive ischemic changes in the CT performed upon the patient's admission and hyperglycemia. (6,7,8)

The administration of rt-PA in a 3-hour normal window or 4.5-hour extended window should be preceded by the evaluation of strict exclusion criteria (see Tables 1 and 2). Systemic fibrinolysis is a *class I indication, Evidence A*.

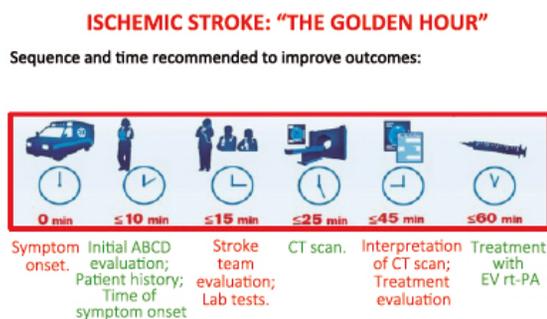
### Mechanical thrombectomy

In the last two years, several studies have shown the benefit of mechanical thrombectomy in patients with arterial obstruction of M1 and persistent intracranial carotid artery after having received the systemic thrombolysis in a window of up to 4.5 hours; *class I indication, Evidence A*. (9,10)

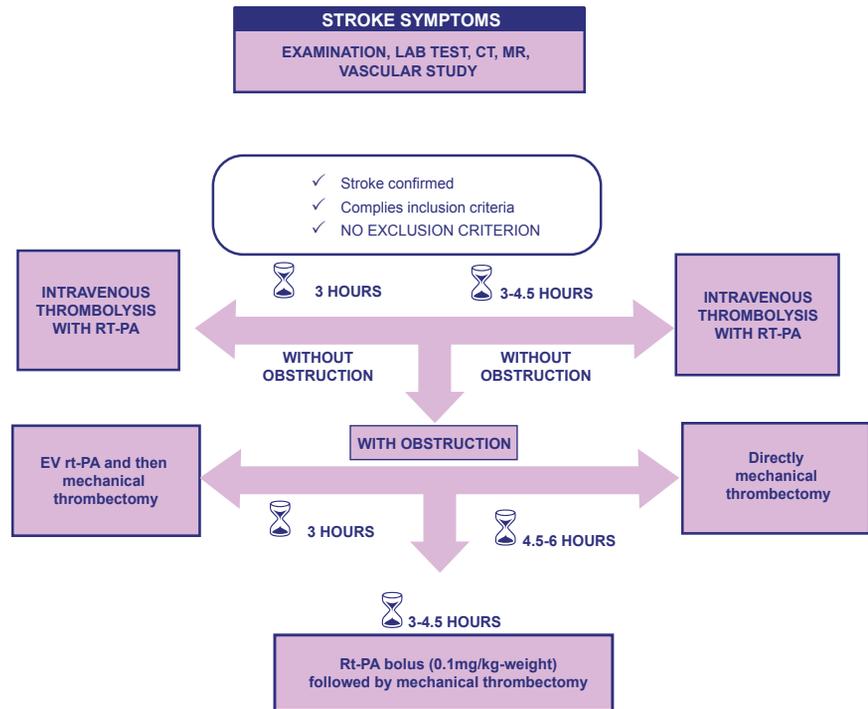
**For the mechanical thrombectomy, the following criteria should be met:**

- 0-1 pre-stroke Rankin scale.
- Stroke of less than 4.5 hours of evolution that has received rt-PA pursuant to the guidelines.
- Occlusion of M1 or intracranial internal carotid artery.
- Patient older than 18 years old.
- NIHSS > 6 points.
- ASPECTS score > 6 points.
- Beginning of treatment within six hours after symptoms onset.

In these studies, *stent retriever*-type devices were used, which showed a higher recanalization level and a lower complication rate *class I Evidence A*. (11)



**Figure 1.**  
Initial management.



**Figure 2.**  
Treatment flowchart

*TABLE 1* Inclusion and exclusion criteria for thrombolysis with 3-hour window.

ELIGIBLE PATIENTS	ABSOLUTE EXCLUSION	RELATIVE EXCLUSION
<ul style="list-style-type: none"> <li>✓ Symptoms onset 3 hours prior to treatment.</li> <li>✓ Age ≥ 18 years old.</li> </ul>	<ul style="list-style-type: none"> <li>• Severe TBI or stroke within previous 3 months.</li> <li>• Suggestive SAH symptoms, even with normal CT.</li> <li>• Non-compressible artery puncture in situ within previous 7 days.</li> <li>• Intracranial bleeding history.</li> <li>• Intracranial neoplasia, AVM or aneurysm.</li> <li>• Recent intracranial or intraspinal surgery (previous 3 months).</li> <li>• High blood pressure (SBP &gt; 185 mmHg or DBP &gt; 110 mmHg).</li> <li>• Active internal bleeding.</li> <li>• Hemorrhagic diathesis: platelets &lt;100,000/mm<sup>3</sup>, prior treatment with heparin with long-term KPTT, prior treatment with oral anticoagulants with INR &gt; 1.7 and TP &gt; 15 seconds, current use of new anticoagulants (dabigatran, rivaroxaban o apixaban)</li> <li>• Blood sugar &gt; 400 mg/dl or &lt; 50 mg/dl.</li> <li>• CT showing multilobar infarction (hypodensity &gt;1/3 of the MCA area)</li> </ul>	<ul style="list-style-type: none"> <li>o Minor stroke symptoms or of quick improvement.</li> <li>o Pregnancy.</li> <li>o Seizure at the onset with postictal residual neurological deficits.</li> <li>o Major surgery or severe trauma within previous 14 days.</li> <li>o Recent gastrointestinal or urinary tract bleeding (within previous 21 days).</li> <li>o Recent AMI (within previous 3 months).</li> </ul>

TABLE 2 Inclusion and exclusion criteria with 4.5-hour window.

ELIGIBLE PATIENTS	RELATIVE EXCLUSION CRITERIA
<ul style="list-style-type: none"> <li>✓ Symptoms onset 4.5 hours prior to treatment.</li> <li>✓ Age &lt; 80 years old.</li> </ul>	<p><i>The same criteria for the 3-hour window with the following changes to be excluded:</i></p> <ul style="list-style-type: none"> <li>• Age &gt; 80 years old.</li> <li>• Stroke severity: NIHSS &gt; 25 points or hypodensity &gt; 1/3 MCA.</li> <li>• History of OCP use, regardless of INR value.</li> <li>• Combination of diabetes + stroke history.</li> </ul>

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## **I) CONTROVERSY I: CARDIAC SURGERY AND CAROTID DISEASE**

Even nowadays, some controversies arise at the time of treating patients with carotid disease and stroke in the context of a central concomitant cardiac surgery. It is also questionable if the endarterectomy or the carotid stenting significantly reduce the risk of ischemic stroke, especially in asymptomatic patients. This is mainly due to two reasons. The first one is that sometimes the causal relation between carotid stenosis and post-cardiac surgery ischemic stroke is difficult to identify. Some observe that the prophylactic endarterectomy would be performed in a reduced group of patients. (1) In most cases, carotid atheromatous disease would behave as a marker in the context of its vascular risk factors and ischemic stroke could be the result of aortic arch plaques during extracorporeal circulation (2-3) or secondary to the presence of postoperative arrhythmias, since up to 30% of patients show an AF (4-5). Second, the variability of the studies conducted, the age of the population under study, inaccurate patient inclusion and exclusion criteria, countless strategies to avoid ischemic stroke, both from the specific point of view of the surgical procedures to be performed (aortic cannulation, non-circulatory assistance surgery, oxygenators, arterial filters, etc.) and the carotid disease (optimization of medical treatment, anticoagulants, carotid stenting, endarterectomy, etc.) affect the number of neurological complications and hinder the proper interpretation of results. While some observational studies show acceptable outcomes in combined surgery (6), others do not succeed in doing so (7). Neurological complications associated with cardiovascular surgery are frequent, causing great morbidity, mortality and disability. These may be divided into type 1, which includes stroke, stupor and coma, and type 2, which refers to those affecting the cognitive function with memory impairment, orientation and/or confusion. Alterations in neuropsychological tests are common, with an incidence that ranges from 30% to 80%. (8) Intermediate manifestations are difficult to categorize.

Global stroke incidence associated with cardiac surgeries varies. Authors refer to values that range between 2.0% and 1.4%, depending on the kind of study (prospective and retrospective). (9)

The non-identification of the patients observed in the different studies should be highlighted. In many cases, neither previously

symptomatic or asymptomatic patients nor their bilateralism and rate of occlusion or partial stenosis are distinguished. In many of these situations (for example, full carotid occlusions), it is already known that endarterectomies or carotid stenting are not very useful. Patients with bilateral lesions would imply higher risk. In cases of asymptomatic carotid stenosis, it has not been observed an increase in the percentage of neurological complications or ipsilateral stroke related to cardiac surgery with extracorporeal circulation (ECC). (9) A meta-analysis found prevalence of stroke, death, and combined stroke and death in patients who underwent cardiac surgery and with carotid lesions higher than 50%, which were not subject to prophylactic endarterectomy of 7.4%, 4.8% and 8.3%, respectively. For patients with lesions between 80-99%, the incidence increased to 9.1%. However, these outcomes combine many of the cases that cannot be revascularized, thus increasing the risk of stroke. (11) Patients with neurological symptoms previously informed (transient ischemic attack or stroke) and with unilateral or bilateral occlusive lesions (and who would not benefit from prophylactic treatment) should be excluded. Throughout his review, Naylor details the risk of death, stroke (30 days) and prevalence of death/perioperative stroke in patients with carotid lesions between 50% - 99% and without prophylactic treatment, with 3.8% in each of the groups. (10)

Nevertheless, most strokes related to the performance of an open cardiac surgery would not seem to be associated with concomitant carotid stenosis. In cases of asymptomatic carotid stenosis, no increase in the percentage of ipsilateral neurological complications related to the cardiac surgery was observed. The causes of stroke in this context may be multifactorial, not only depending on the carotid lesion. Macro and micro embolization phenomena may be the result of surgical manipulation of the aorta or the heart chambers. Likewise, hypoperfusion phenomena may have a prevailing role. However, in cases of severe bilateral carotid stenosis, encephalic hypoperfusion may not occur during ECC. (12,13)

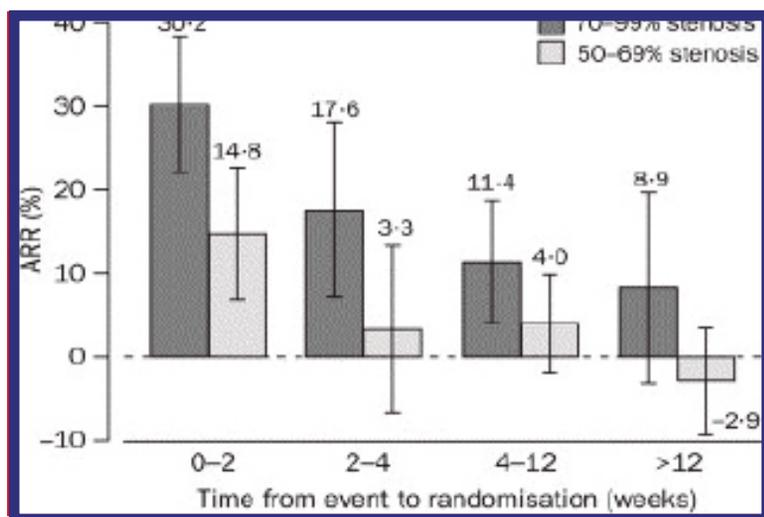
So far, there is no evidence that the endarterectomy benefit patients with asymptomatic carotid disease who must undergo a coronary surgery. (14) Some data suggest that combined surgery implies higher procedural risk (15) and thus, in most cases, a staged carotid procedure is preferred over cardiac surgery. Under these circumstances, the endarterectomy would be prioritized over stenting, since the latter would imply a greater delay for coronary acute revascularization due to the antiplatelet therapy and a higher risk of bleeding after cardiac surgery. The use of endovenous heparin *post-stenting* until cardiac surgery has not been tested. As this circumstance is accepted, stenting should not be considered a first strategy. (16)

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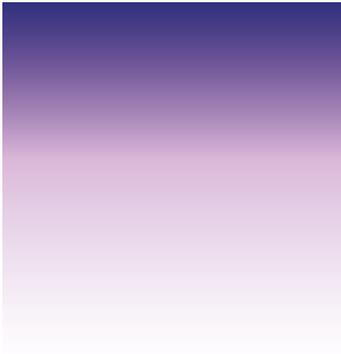
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## II) CONTROVERSY II: TIME FOR SURGERY IN PATIENTS WITH SYMPTOMATIC CAROTID ATHEROMATOUS DISEASE

The role of carotid artery endarterectomy (CAE) in symptomatic patients with extracranial carotid artery disease has been firmly established since the publication, during the 1990s, of the classical studies North American Symptomatic Carotid Endarterectomy Trial (NASCET) <http://www.elsevier.es/es-revista-angiologia-294-articulo-endarterectomia-carotidea-precoz-versus-diferida-90359406-bib1> and European Carotid Surgery Trial (ECST). (1,2) However, the time for the performance of a CAE after a neurological event has become a subject of controversy. Historically, literature had suggested that, after a stroke, a CAE needed to be performed 6 weeks following the ischemic event (3) to minimize the risk of postoperative complications such as brain edema and possible postoperative bleeding of the previous stroke. However, in 2004, the publication of a subgroup reanalysis of the NASCET and ECST studies (4) marked a turning point, questioning the historical paradigm that defers the CAE 6 weeks after the stroke. This study had concluded that patients with  $\geq 70\%$  symptomatic carotid artery stenosis benefited more if operated on within the first 2 weeks after the stroke.



Early surgery within the first 14 days after the stroke is the most effective measure to reduce the risk of new events in symptomatic patients (Class II Evidence A). Clinical conditions that may be limited by this indication are: post-stroke bad neurological condition (patients with consciousness deterioration, severe focal neurological deficit, extensive ischemic lesions, with edema or bleeding transformation or patient's clinical instability). ■



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