Recommendations and treatment strategies for the management of acute ischemic stroke

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Background: Stroke is one of the leading causes of mortality and disability worldwide. From the establishment of the penumbra concept, ischemic stroke has been recognized as a dynamic process and two main therapeutic strategies have been designed: one that tries to reopen the occluded artery and the second aims to protect the penumbra brain tissue until the physiologic mechanisms—or the treatment—stop the ischemia. Objective: To review the most recent, high-quality evidence for acute stroke treatment. Methods: Systematic review of relevant published studies focused in several aspects of acute ischemic stroke management, from neuroprotection to thrombolysis. Conclusions: After the publication of NINDS rt-PA study, the classical nihilistic approach to ischemic stroke started to change and thrombolytic treatment was approved in the treatment of patients with acute ischemic stroke presenting within 3 h from onset of symptoms. Advances in this field are proceeding on several fronts, including the use of next-generation plasminogen activators and glycoprotein IIb/IIIa inhibitors, refined patient selection with advanced magnetic resonance imaging sequences, endovascular approaches to thrombolysis and thrombectomy, and adjuvant use of ultrasound. Abrupt deprivation of oxygen and glucose to neuronal tissues elicits a series of pathologic cascades, leading to the spread of neuronal death. Of the numerous pathways identified, excessive activation of glutamate receptors, accumulation of intracellular Ca²⁺ cations, abnormal recruitment of inflammatory cells, excessive production of free radicals and initiation of pathologic apoptosis are believed to play critical roles in ischemic damage, especially in the penumbral zone. Several neuroprotective agents designed to block these cascades have been investigated in animal models of cerebral ischemia and numerous agents have been found to reduce infarct size. However, translation of neuroprotective benefits from the laboratory bench to the emergency room has not been successful. Other measures, such as the relevance of body position in the acute phase of stroke, anticoagulant and antiplatelet agents or the effects of statins and antihypertensive therapy, are discussed in this paper, with an overview of the relevance of stroke units.

Keywords: clinical trial, ischemia, neuroprotection, stroke management, thrombolysis

1. Introduction

Stroke is one of the leading causes of mortality and disability worldwide. Annually, 15 million people suffer a stroke, with 5 million of those resulting in death and a further 5 million left with permanent disability. Most strokes (~80%) are ischemic in nature and several etiologies may be identified, including strokes due to large vessel atherosclerosis, small vessel disease, cardioembolism or other multiple
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potential causes. However, acute stroke management does not only depend on its different causes but on a better understanding of its pathophysiology. The most important advance in this direction was the demonstration in 1981 of the so-called ‘penumbra area’ surrounding the ischemic core [1]. This area is a rim of moderately ischemic tissue with impaired electrical activity, but preserved cellular metabolism and viability. The fate of this tissue is uncertain: the final size of the infarction depends on multiple circumstances, such as the existence or lack of collateral circulation, previous health of the ischemic tissue, ‘local environment’ (excitotoxicity, inflammatory response and other conditionings) and even the genetically codified response to ischemic insult. From the establishment of the penumbra concept, ischemic stroke is recognized as a dynamic process and not just as an irreversible process resulting in the ultimate death of neurons. The enormous diversity of variables that could influence ischemic stroke evolution raises a great theoretical diversity of therapeutic options. Unfortunately, in spite of the large amount of knowledge acquired over the last 25 years, there are still very few treatments with proven clinical efficacy to fight against stroke. In this review, the authors analyze the approved therapies as well as some of the latest trials that try to open up new therapeutic possibilities. As there are two main therapeutic strategies, one that tries to reopen the occluded artery and the second that aims to protect the penumbra brain tissue until the natural physiologic mechanisms or the treatment stop the ischemia, the authors have divided the text among these two main approaches and added a third point to review other modalities of treatment.

2. Neuroprotection

Critical decrease in focal cerebral blood flow following a vessel occlusion promotes a complex biochemical cascade in the ischemic tissue that interferes with glucose metabolism and causes cell sodium pump failure. This leads to neuron depolarization and the release of excitotoxic neurotransmitters that are able to cause abrupt necrotic cell death in the infarct core. But in the surrounding tissue, the penumbra area, a dynamic process starts. This process also involves intracellular calcium influx, free radicals production, expression of adhesion molecules leading to inflammation and activation of apoptosis. Programmed cell death probably has the leading role in the evolution of the penumbra area, given that neuronal death takes place principally in this region via apoptosis. Besides the morphologic and biochemical differences between necrosis and apoptosis, the main differential characteristic is that apoptotic pathways allow pharmacologic intervention at the three established stages of programmed cell death: activation; commitment; and execution (Figure 1). In the first stage, excitotoxic process, calcium ion concentrations rising and reactive oxygen species formation promote apoptotic gene expression. Through a process mainly regulated by changes in the permeability of their outer membrane, mitochondria play a central role in the commitment stage, being considered the non-return point. Finally, in the execution stage, degradation enzyme complexes, such as caspases, calpains and endonucleases, take part. It is considered that it is possible to avoid neuronal damage only by preventing the first two stages

![Figure 1. The stages of apoptosis.](image-url)

ROS: Reactive oxygen species.
because acting on the execution stage can delay cell death, but does not block it. The authors review the different strategies that potentially could abort cell death in the ischemic brain tissue (Figure 2).

2.1 Interfering with excitotoxicity process
2.1.1 Glutamate receptor antagonists
Excitotoxicity plays an important role as a cause of neuronal death in stroke [2]. This excitotoxicity is mainly mediated by several glutamate receptor subtypes, including NMDA and AMPA receptors. NMDA receptor antagonists were the first neuroprotective agents tested in stroke clinical trials. Unfortunately, no efficacy or unacceptable side effects were found both with competitive NMDA antagonists (seftotel) and non-competitive NMDA antagonists (dextrorphan, aptiganel and eliprodil). Activation of the NMDA receptor requires the co-agonist glycine. Studies of the glycine antagonist gavestinel found that medication was safe but favorable outcomes were not found. Another glycine antagonist, licostinel, was associated with numerous side effects.
The AMPA receptor is the principal mediator of fast excitatory neurotransmission. This ligand-gated cation channel is primarily permeable to sodium rather than calcium. In a variety of animal models, reduction in infarct volume with AMPA blockade has been demonstrated. First-generation AMPA receptor blockers were competitive antagonists, such as 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX), which showed robust neuroprotection in a variety of disease-related animal models. However, its clinical use was restricted by the very low solubility, which induced kidney precipitation in vivo. Second-generation competitive antagonists are available, which do not possess this property. However, none of those up to now is in clinical use. The AMPA antagonist ZK 200775 led to neurologic worsening in a preliminary study. A novel, highly water-soluble, competitive AMPA receptor antagonist, YM872 (zonampanel), has been identified. Phase I studies showed YM872 was well tolerated at 1.25 mg/kg/h when given as a 24-h infusion to healthy subjects. Sedation and other CNS-associated adverse events determine the ceiling dose and become more problematic with infusion times exceeding 24 h. A Phase II trial of YM872 in acute ischemic stroke is ongoing.

A systematic review of trials testing excitatory amino acid antagonists in stroke [3] found no improvement in rates of either death or favorable outcomes with treatment.

2.1.2 GABA agonists
Clomethiazole, a GABA agonist with the property of increasing cellular resistance to glutamate toxicity, was tested in the clinical trial CLASS (Clomethiazole Acute Stroke Study). This trial was unable to show efficacy and a subsequent study restricted to patients with total anterior circulation syndrome also failed to show benefit [4].

2.1.3 Other agents
Magnesium has multiple potential actions: it can block NMDA receptors; inhibits presynaptic excitatory neurotransmitters release; and antagonise voltage-sensitive calcium channels. Due to all these actions, it was thought that this agent could be useful in the reduction of ischemic brain injury. However, the international Phase III IMAGES (Intravenous Magnesium Efficacy in Stroke) trial investigating the efficacy of magnesium in stroke did not find benefit [5]. Most patients in this study received magnesium beyond 3 h. As so, the investigators of the pilot study FAST-MAG (Field Administration of Stroke Therapy-Magnesium) planned a scaled-up, randomized, controlled trial to test magnesium efficacy when the drug was administered in a hyperacute stage [6]. Patients received paramedic-administered magnesium an average of 26 min after stroke onset with safe results. Clinicians noted patient improvement in 20% of cases, deterioration in 7% and no change in 73%. A FAST-MAG Phase III trial is ongoing to evaluate the efficacy of hyperacute, paramedic-initiated magnesium sulfate administration in improving the long-term functional outcome of patients with acute stroke.

2.2 Sodium channel blockers
2.2.1 Lubeluzole
Lubeluzole is a sodium channel blocker with additional effects on nitrous oxide. Although a pilot study suggested that this agent was safe and might reduce death rates in stroke, subsequent clinical trials found no effects in reducing deaths or improving outcomes [7].

2.2.2 Others
Fosphenytoin is a well-known anticonvulsant agent that blocks sodium channels and prevents glutamate release. However, its clinical efficacy in ischemic stroke has not been demonstrated.

Sipatrigine (619C89), a sodium and calcium channel blocker, did not have any favorable effects on outcome measures in a Phase II clinical trial using a continuous intravenous infusion of this agent in acute stroke [8].

2.3 Calcium channel blockers
Voltage-dependent Ca\(^{2+}\) channels (L-, N-, T-, P- and Q-type) have been widely recognized as important regulators for the nervous system. Blockade of N-type Ca\(^{2+}\) channels can suppress the pathologic process in animal models of ischemic brain injury. Another possibility is blocking the intracellular increase of calcium. Previous Phase I and II trials indicated that the calcium chelator DP-b99 may be safely administered to stroke patients. Phase IIa trials have shown significant improvements in clinical stroke outcome in patients treated within 12 h of symptoms onset. There is an ongoing Phase III trial that will aim to confirm the safety and efficacy of this agent.

2.4 Antioxidants
Considerable evidence suggests that reactive oxygen species (ROS), which are generated when blood flow returns to ischemic brain areas, are mainly responsible for the reperfusion injury. Deleterious ROS are produced by the mitochondrial electron transfer chain and by a wide variety of enzymes. Compounds with free radical-scavenging activity (tirilazad and ebselen), iron chelator (deferoxamine [DFO]) or free radical-trapping properties (NXY-059) have been examined in experimental models of stroke and evaluated clinically as neuroprotective agents.

Preclinical data on tirilazad in animal models of acute ischemic stroke were neither comprehensive nor consistent. Therefore, when studied in humans, tirilazad not only did not improve outcome after stroke but appeared to marginally worsen it [9]. On the other hand, ebselen, a selene organic compound with antioxidant activity, might be safe and effective in improving outcomes after acute ischemic stroke as a dose-escalation study suggested [10]; another clinical trial is under way.

The neuroprotective potential of the iron chelator DFO comes from its antioxidant effect as well as its capacity to stabilize the hypoxia-inducible factor-1 (HIF-1)
protein expression. HIF-1, one of the main transcriptional factors regulated by the level of oxygen, increases the expression of several beneficial genes such as erythropoietin, glucose transporter-1 and VEGF. In animal models, treatment with DFO significantly decreased the size of brain damage after ischemia and improved behavioral and sensorimotor recovery. The safety of DFO in acute stroke patients > 50 years old without known iron overload is being currently tested.

The NXY-059 compound (Cerovive®; AstraZeneca) has been proposed to act as a free radical scavenger and was effective in reducing lesion volume and neurologic deficits. The positive results from the first SAINT (Stroke-Acute-Ischemic-NXY-Treatment-I) trial, which followed many of the Stroke Therapy Academic Industry Roundtable (STAIR) guidelines, reinvigorated the enthusiasm for neuroprotection [11]. The STAIR recommendations seek to improve the quality of preclinical research and to ensure that the data generated will enable the selection of those agents that are most suitable for progression from the laboratory into clinical trials. However, the recently published SAINT-II trial has failed to confirm the efficacy of NXY-059 in acute ischemic stroke treatment, adding a new disappointment in the search of clinically effective agents that are most suitable for progression from the laboratory into clinical trials.

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### 2.5 Membrane stabilizers

Citicoline is a key intermediary in the biosynthesis of the important component of the neural cell membrane phosphatidylcholine and has shown antia apoptotic effects in cerebral ischemia. In a meta-analysis by pooling the individual patients’ data from several clinical trials in acute stroke, citicoline showed a significant increase in the odds of recovery at 3 months compared with placebo [13].

A new multicenter pivotal study, the ICTUS (International-Citicoline-Trial-on-Acute-Stroke) trial, is in progress to confirm these results.

### 2.6 Modulating transcription factor activity

The activation of some transcription factors has been detected in neurons and microglia in the penumbra area. These include HIF-1 (see Section 2.4), p53 and PPARs.

The p53 protein, also known as ‘guardian of the genome’, is activated on stress signals, such as hypoxia and DNA damage. The regulation of p53 functions is tightly controlled through several mechanisms including p53 transcription and translation, protein stability, post-translational modifications and subcellular localization [14]; therefore, p53 can be considered a pharmacologic target. Blocking p53 expression demonstrably and efficiently protects against cerebral ischemia in experimental models, and this protection includes a reduction in rates of apoptosis [15]. Indeed, preclinical studies demonstrate the efficacy of a p53 inhibitor in models of stroke and neurodegenerative disorders, and suggest that drugs that inhibit p53 may reduce the extent of brain damage in related human neurodegenerative conditions.

PPARs are endogenous protective factors in cerebral ischemia. Activation of PPAR-γ with pioglitazone or a thiazolidinedione might also reduce immune reactions and at the same time reveals a powerful anti-inflammatory potential in ischemic brains. Activation of PPAR-γ attenuates the expression of ICAM-1 (intercellular adhesion molecule-1), matrix metalloprotease-9 (MMP-9) and various cytokines in ischemic brain tissue. Furthermore, PPAR agonists decrease the expression of COX-2, an enzyme involved in the production of ROS, and increase the expression level of the ROS scavenger CuZn superoxide dismutase. The PPAR-γ agonist rosiglitazone would be a potential novel therapeutic agent for stroke [16].

### 2.7 Mitochondria

Mitochondria are considered the main link between cellular stress signals and the execution of programmed nerve cell death [17]. Translocation of cytochrome c (Cyt c) from mitochondria to the cytoplasm is a key step in the initiation and/or amplification of apoptosis. Calcium-induced Cyt c release, as occurs in neurons during stroke and ischemia, involves rupture of the mitochondrial outer membrane and can be blocked by inhibitors of the mitochondrial permeability transition pore (MPTP). MPTP blockers, such as cyclosporin A (CsA) and bongkrekic acid, have shown neuroprotective effects in animal models of ischemia. Several inhibitors of Cyt c release have shown promise in models of CNS apoptosis [18].

### 2.8 Others

#### 2.8.1 Downregulation of the levels of circulating homocysteine

An overview of observational epidemiologic studies reveals an independent, linear relationship between increasing levels of homocysteine and risk of stroke [19]. The VISP (Vitamin Intervention for Stroke Prevention) trial was designed to determine if a multivitamin containing high-dose folic acid, pyridoxine and cobalamin given with the aim of lowering total homocysteine levels would reduce the incidence of recurrent cerebral infarction (primary outcome) as well as coronary heart disease (CHD) and death (secondary outcomes). The trial showed that moderate reduction of total homocysteine after non-disabling cerebral infarction had no effect on vascular outcomes during the 2 years of follow-up [20]. In the same way, the VITATOPS (Vitamins to Prevent Stroke) trial aims to determine whether lowering plasma homocysteine concentrations by the administration of vitamin supplements will reduce the sequelae following brain ischemia.

#### 2.8.2 Arundic acid

Arundic acid (AA; ONO-2506), a novel modulator of astrocyte activation, may improve neuronal survival after...
stroke by suppressing S-100β protein production in astrocytes. In the presence of ischemia or other biochemical insults, S-100β protein is overexpressed in astrocytes and, in turn, induces mRNA expression of inducible nitric oxide synthase (iNOS), nerve growth factor (NGF),β and COX-2. AA reduces cerebral infarct volume and improves neurologic function in rodent surgical models of acute ischemic stroke. AA is active in a wide time window after the onset of neurologic injury as astrocyte activation occurs over many hours in both human stroke patients and preclinical stroke models. In seven completed Phase I healthy-volunteer studies and two previous stroke-patient safety studies, AA was well tolerated. The efficacy of AA in acute stroke treatment should be confirmed in future clinical trials [21].

2.8.3 Albumin
Preclinical studies have suggested that albumin has potentially neuroprotective effects including haemodilution, binding to free fatty acids, oxygen free radical production inhibition, endothelial function improvement, platelet activation inhibition and microvascular patency maintenance [22]. Recent data from a Phase I dose-escalation study [23] provide evidence that human serum albumin is safe after stroke even when given with thrombolytic therapy, despite an increase in mild-to-moderate pulmonary edema. The study provided preliminary evidence of efficacy with patients in the highest-dose tiers having an ∼ 80% greater chance of good outcome at 3 months than patients in the lower-dose tiers [24]. There also seemed to be a synergistic effect between albumin and thrombolytic therapy. A recently published Phase I/II clinical trial confirmed the clinical benefit of albumin administered within 24 h from symptom onset, showing that these effects were dose- and time related [25]. A more definitive Phase III trial (Albumin-in-Acute Stroke) is underway.

2.8.4 Hypothermia
The potential for neuroprotection of hypothermia has long been suspected. Victims of near drowning in ice-cold water can have a remarkable neurologic recovery even after prolonged cerebral ischemia [26]. The precise mode of neuroprotective action in hypothermia is not known; it is most likely that hypothermia exhibits multiple and synergistic effects on brain metabolism. Hypothermia decreases the cerebral metabolic rates of glucose and oxygen, and slows ATP breakdown [27]. In the range of 22 – 37°C, brain oxygen consumption is reduced by ∼ 5% for every degree fall in body temperature. Hypothermia reduces glutamate release [28], inflammation and free-radical generation. It also lowers metabolic rate, limits edema formation and interrupts necrosis/apoptosis [29,30]. In addition, hypothermia reduces the intracellular calcium rise after ischemia due to the impairment of glutamate-mediated calcium influx or directly inhibiting calcium-mediated effects on calcium/calmodulin kinase [30].

In the course of the last 15 years, a variety of experimental animal studies in global and focal cerebral ischemia indicated that mild and moderate hypothermia (∼ 32 – 34°C) are successful for improving neurologic outcome and decreasing the size of a cerebral infarct. Consequently, clinical interest was renewed and the method was used during open-heart surgery, after cardiac arrest and in the management of traumatic brain injury [31,32]. Although infarct size was reduced in most models, animals with moderate hypothermia experienced greater recovery than those with severe hypothermia [33], which may be caused by a reduction of regional cerebral blood flow at very low temperatures.

Some pilot studies have shown feasibility of mild and moderate hypothermia in stroke. In a pilot trial [34], treatment with paracetamol 6 g/day compared with placebo led to a 0.3°C reduction in body temperature in normothermic patients, which is of potential but unproven clinical benefit. In another study [35], 40 patients were randomly assigned either to standard care or endovascular intravenous cooling to 33°C for 24 h within 12 h of symptom onset. Hypothermia was well tolerated, but clinical and MRI measures did not differ between treatment groups.

The advantages of surface cooling are such that it does not require advanced equipment or expertise in catheter placement, and averts the risk associated with central venous catheter placement. However, cooling through external methods requires many hours to reach and maintain a temperature < 35°C and, in most cases, necessitates the use of sedatives and paralytics to prevent discomfort and shivering. In addition, cooling of the skin leads to vasoconstriction and reduces the heat exchange in cooled patients, which makes temperature control very difficult. This may lead to target temperature overshoot and lack of control during passive re-warming, which may be associated with reactive brain edema. In patients who are awake, surface cooling is only achieved as an approach for mild hypothermia and fever control. New surface-cooling devices, such as energy-transferring skin pads [36], may demonstrate a reduction in the time to target temperature and allow better temperature control.

Further studies are needed to determine whether hypothermia improves outcome. The use of hypothermia might also be limited by its substantial side effects (including shivering and infections) and by practical considerations (including the need for treatment in an intensive care unit).

3. Reperfusion

3.1 Intravenous thrombolysis
The aim of reperfusion treatment is to restore cerebral blood flow and the main clinical tools to achieve this objective are thrombolytic drugs. These agents enhance the endogenous formation of fibrinolysin from plasminogen, which can dissolve the blood clot occluding a cerebral vessel via the
disruption of fibrin. Until 1996, several attempts had been made to find a thrombolytic drug that is as useful in ischemic stroke as in myocardial infarction but were not successful. In 1996, recombinant tissue plasminogen activator (rt-PA, alteplase) was granted FDA approval largely on the basis of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA study [37]. In this pivotal study, 624 patients were randomly assigned to treatment with intravenous rt-PA or placebo. There was a significant increase in the likelihood of favourable outcome (defined as Barthel Index 95-100, modified Rankin scale < 2, NIHSS < 2 and Glasgow Outcome Scale = 1) in the patients who received rt-PA. The study only included patients treated within 3 h of symptoms onset and ~50% were treated within 90 min. Until now, intravenous rt-PA remains the only thrombolytic agent currently licensed to treat selected patients with acute ischemic stroke. However, in the EU, regulatory authorities did not approve the use of rt-PA until 2002; at that time, it was limited to a restricted licence in specialist centers. This special regulation in Europe is probably influenced by the unsuccessful results of the European Cooperative Acute Stroke Studies (ECASS and ECASS II) [38,39]. In these two large trials, intravenous rt-PA was no more effective than placebo in improving neurologic outcome 3 months after stroke. It is very likely that time was a significant factor implicated in the results of the ECASS studies as the patients in these trials were treated ≤6 h after stroke. However, a post-hoc analysis concluded that patients treated within 3 h appeared to benefit from rt-PA treatment and, in fact, community studies have confirmed the safety and usefulness of the drug in the first 3 h after stroke onset in routine medical practice [40-42]. The recently completed SITS-MOST (Safe Implementation of Thrombolysis in Stroke Monitoring Study) study was designed to evaluate the safety and efficacy of intravenous rt-PA within 3 h of symptoms onset in acute ischemic stroke patients under routine clinical use. This large international, multicentre, open study has confirmed the safety and efficacy of rt-PA within this timeframe [43]. The outcome data of the study give substantial credence to the treatment results previously seen in randomized trials; however, uncertainty remains regarding the usefulness of rt-PA beyond 3 h of stroke onset. It seems that the poor results of alteplase beyond this temporal window are not a consequence of a significant increase of hemorrhagic transformation (HT) but of a lesser effect over the ischemic tissue, probably because most of the penumbra area has already been irreversibly damaged (Figure 3). In the early 1980s, several trials using streptokinase had to be stopped due to a large proportion of HT in the treatment group [44,45]. In ECASS studies, however, treatment with rt-PA was not associated with death nor did it cause an unacceptable proportion of HT, but simply proved to be ineffective when administered beyond 3 h. A combined analysis of six randomized controlled trials of intravenous rt-PA [46] showed that the sooner patients received thrombolytic therapy, the greater the benefit. This same analysis found that the benefit in acute stroke seemed to disappear 4.5 h after the onset. A new Phase III trial, ECASS 3, is currently underway and deals with the specific question: is intravenous alteplase effective between 3 and 4.5 h after stroke onset? However, although efficacy of thrombolytic agents is highly influenced by time, it depends on other conditions. ‘Not Only Time Is Brain’ and probably some patients have no salvageable tissue before the 3 h limit. More interesting is that some other patients could still benefit from any treatment capable of restoring blood flow beyond this period of time. This is a paramount circumstance given that, even in dedicated centers, no more than 4 – 8% of stroke patients receive intravenous rt-PA with the present limitations. Less restrictive time criteria for thrombolysis could increase eligibility for treatment. Advanced hospitals are using MRI for selecting patients for thrombolysis beyond 3 h after symptoms onset. The perfusion-weighted imaging diffusion-weighted imaging (PWI-DWI) mismatch is thought to represent tissue at risk of infarction but is potentially salvageable tissue. This mismatch is found in ≥60% of stroke patients examined within 12 h and is a strong predictor of infarction growth. The DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) study [47] provided the stronger indication that, for stroke patients treated 3 – 6 h after onset with thrombolytics, baseline MRI findings (mismatch) can identify subgroups that are likely to benefit from reperfusion and can potentially identify subgroups that are unlikely to benefit or can be harmed. Beyond the 6-h limit, a Phase II double-blind placebo-controlled trial showed that desmoteplase, a thrombolytic agent derived from the saliva of the vampire bat Desmodus, administered 3 – 9 h after stroke onset in patients with PWI-DWI mismatch was associated with a better clinical outcome [48]. Although it is probable that part of the efficacy of desmoteplase lies in its pharmaceutical properties (higher fibrin specificity and absence of NMDA-mediated neurotoxicity), the DIAS (Desmoteplase in Acute Ischemic Stroke Trial) results suggested that thrombolysis might be safe beyond 3 h if suitable patients were selected. This finding encouraged stroke investigators with the hope that it would be possible in the near future to extend the therapeutic window far beyond 3 h. Anyway, it has recently been announced that the larger, prospective clinical trial DIAS-2 does not reproduce the positive effects of the previous DIAS study. The scientific community is waiting for the published data but it is probable that new trials testing desmoteplase or other thrombolytic agents will be necessary in the following years to select and treat acute stroke patients beyond the present restrictive 3-h limit.

Finally, a further strategy to improve intravenous thrombolysis response is predicting and preventing the risk of hemorrhagic transformation. Thrombolytic drugs may have deleterious effects related in part to matrix proteolysis within the neurovascular...
unit. MMPs are upregulated after brain ischemia, degrade the basal lamina and disrupt the blood–brain barrier favoring edema and HT \[49\]. Therefore, new approaches to improve intravenous thrombolysis may include the finding of new agents that do not promote MMP disregulation or agents that are able to block the MMP effects. Until then, several biomarkers such as plasma MMP-9 or cellular fibronectine have shown its value in predicting HT with a sufficient sensitivity and could be used to select candidates for rt-PA thrombolysis \[50,51\].

3.2 Ultrasound enhanced thrombolysis
Ultrasound can induce microstreams within the clot, resulting in a better distribution of rt-PA to facilitate lysis. In contrast to the increased rate of intracranial hemorrhages observed in stroke patients treated with intravenous rt-PA plus low-frequency (300 KHz) ultrasound monitoring in the TRUMBI (Transcranial Low-Frequency Ultrasound-Mediated Thrombolysis in Brain Ischemia) trial \[52\], the CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic TPA) trial has demonstrated that continuous 2-MHz transcranial Doppler ultrasound monitoring of an acute intracranial artery occlusion safely leads to an absolute 20% increase in the rate of middle cerebral artery (MCA) recanalization in stroke patients \[53\]. Moreover, preliminary data show that the administration of ‘microbubbles’, small air- or gas-filled microspheres with specific acoustic properties, could be used to further enhance high-frequency (2 MHz) ultrasound-augmented thrombolysis in acute ischemic stroke \[54\].

3.3 Intra-arterial thrombolysis and combined therapy
Intra-arterial (IA) thrombolysis has been shown effective up to 6 h after symptom onset in MCA occlusions \[55\]. Although no trials have compared IA and intravenous thrombolysis, some indirect data suggest a higher rate of recanalization with the IA approach. But, given that IA treatment requires the patient to be at an experienced stroke center with immediate access to cerebral angiography and qualified interventionalists, the common agreement between clinicians is to recommend IA thrombolysis as an option for the treatment of selected patients who have major stroke of < 6-h duration due to occlusions of the MCA and who are not otherwise candidates for intravenous rt-PA. Moreover, a combined intravenous and IA approach has been proposed \[56\]: this protocol combines the advantages of intravenous (speed of initiation of therapy as well as widespread availability) and IA rt-PA therapy when possible (mechanical aids to recanalization and possibly superior and earlier recanalization power). Currently, the IMS (Interventional Management of Stroke) III trial is comparing a combined intravenous and IA treatment.
approach to the standard approach of giving intravenous rt-PA in 40 centers in the US and Canada.

3.4 Fibrinogen-depleting agents
Fibrinogen-depleting agents reduce fibrinogen in blood plasma, reduce blood viscosity and increase blood flow. Ancrod is an enzyme derived from snake venom that degrades fibrinogen and has been the better-studied defibrinogenating agent. Ancrod has proved that it is capable of moderately reducing the proportion of patients who were dead or disabled after an ischemic stroke when used in the first 3 h after stroke onset. Further studies of ancrod continue, given the potentially favorable combination of antithrombotic activity and mild thrombolytic effect [57].

3.5 Endovascular interventions
Although this area of treatment of acute ischemic stroke shows great promise, limited data are available. Several endovascular interventions are being evaluated. There are some successful reports of angioplasty combined with thrombolysis in patients with occlusions in the verteobasilar circulation, but until now both angioplasty and stenting of intracranial vessels remain anecdotic in the emergency treatment of stroke. Likewise, new advances have been made in mechanical embolus disruption or removal. FDA has recently approved the use of MERCI device (based on the results of the Mechanical Embolus Removal in Cerebral Embolism trial) for reopening intracranial arteries, although its clinical utility has not been established [58]. This option may be particularly interesting for non-responders to drug thrombolysis, in proximal artery occlusions (that is to say, when the intracranial carotid artery as well as its branches middle carotid artery and anterior carotid artery are affected) and for patients who are otherwise ineligible for thrombolytic therapy. In spite of MERCI retriever approval, we must bear in mind that re-establishing brain perfusion alone does not guarantee clinical improvement if reperfused tissue is already irreversibly injured. At the time of writing, there were ongoing trials aiming to select the appropriate therapeutic window for the retrieval devices. The previously mentioned IMS III trial uses FDA-approved devices such as the Concentric Retriever Device® and the EKOS microInfusion Catheter® in the IA treatment approach.

4. Other treatments

4.1 Body position
Measures that promote blood flow during the acute phase of ischemic stroke may directly affect the subsequent development of brain infarction. One such measure may be the flat head-of-the-bed (HOB) positioning to promote a gravity-induced increase in arterial flow to ischemic brain tissue.

Several studies have aimed to identify the optimal HOB position for patients with neurologic disorders. Most of them focused on parameters measuring cerebral perfusion pressure (CPP) more than real-time arterial flow variables. Findings from those studies were inconclusive, with some favoring HOB elevation [59,60], flat positioning [61,62] and positioning guided by individual patient factors [63].

There are only two HOB studies consisting entirely of patients with ischemic strokes and normal intracranial pressure (ICP). In the study from Schwarz et al. [61], MCA mean flow velocity (MFV) data were also obtained using transcranial Doppler (TCD) even though ICP and CPP were the primary variables of interest. This study concluded that, although ICP was higher in a flat position, CPP and MCA MFV were highest when patients were placed in the 0° HOB position. Wojner-Alexander et al. [62] studied patients with an anterior circulation stroke and persistent arterial occlusion with residual flow signals obtainable by TCD within 24 h of symptom onset. Their study showed that decreasing HOB elevation from a height of 30° to the 0° position resulted in a 20% increase on average in the mean velocity of the residual arterial blood flow in the affected artery, without increasing resistance to flow from a potential increase in ICP. Anyway, these studies did not answer the question about the timeframe for which the effect of 0° positioning continued to benefit ischemic stroke patients nor whether a difference in stroke outcome may be derived from this intervention, even in patients with large strokes and massive brain edema.

4.2 Anticoagulant and antiplatelet agents
Several studies have shown no benefit of anticoagulation in acute ischemic stroke [64,65]. Long intervals from onset to treatment have been considered responsible for the absence of effect. However, anticoagulation, even within 3 h, is of unproven benefit [66,67]. Therefore, anticoagulants (such as heparin) have no role in the routine management of acute ischemic stroke. Despite absence of evidence, heparin and heparinoids are still frequently used. According to the American and European guidelines, the use of anticoagulants should be restricted to special cases, such as cerebral venous sinus thrombosis and possibly arterial dissections [68,69].

Acute aspirin has been tested in two large trials. The International Stroke Trial [70] compared aspirin alone with two different doses of heparin within 48 h of symptom onset. Aspirin was associated with significantly fewer recurrent ischemic strokes and no significant increase in hemorrhagic strokes at 14 days. The rate of death or dependency did not differ between the two groups at 6 months. The Chinese Acute Stroke Trial [71] also compared aspirin with placebo within 48 h of symptom onset. Significantly fewer recurrent ischemic strokes occurred in the aspirin group, but the number of hemorrhagic strokes increased. Aspirin given within 48 h of acute ischemic stroke seems to reduce death and disability. However, the use of aspirin in conjunction with alteplase might increase the risk of bleeding [72,73]. Acute aspirin is recommended for patients with acute ischemic stroke who are ineligible for thrombolysis.
Acute clopidogrel loading (300 mg) followed by maintenance (75 mg/day) has proved to be safe and effective in acute coronary syndromes [74], but has not been adequately tested in acute ischemic stroke. Trials assessing abciximab, a glycoprotein IIb/IIIa receptor inhibitor, within 6 h of symptom onset were initially promising [75,76]. Nonetheless, a large Phase III trial was stopped early because of safety concerns [77]. Thus, neither clopidogrel loading nor abciximab can be recommended for acute ischemic stroke outside a clinical trial setting.

4.3 Statin therapy
In addition to preventing primary and recurrent ischemic stroke [78], statins may also be neuroprotective. They have been successfully tested in animal models of acute brain ischemia [79,80] and some observational studies suggest that patients treated with statins before or early after an ischemic stroke have a more favorable outcome. In the National Institutes of Health Suburban Hospital Stroke Program Study, 22% of patients were taking a statin when they were admitted. In this observational study, 51% of patients taking these drugs had a good outcome compared with 38% of those not taking statins [81]. Another study [82] included patients with stroke, 18% of which were using statins when admitted. Favorable outcomes at 3 months were significantly more frequent in the statin group, indicating that these drugs may provide benefits for the long-term functional outcome when administered before the onset of cerebral ischemia. In addition, the preliminary results of a pilot clinical trial have been communicated, suggesting that simvastatin therapy initiated in the acute phase of ischemic stroke might also improve neurologic outcome.

Statin therapy has also been proven to be useful when used in combination with thrombolytic therapy. In an embolic model of cerebral ischemia in rats, the combination treatment with atorvastatin and rt-PA exerts a neuroprotective effect when administered 4 h after stroke [83]. In clinical practice, a recent study has evaluated 145 patients with a stroke involving the MCA who received rt-PA treatment [84]; among patients who were functionally independent at 3 months, 27.3% were taking statins at the time of the index stroke compared with 13.6% among the group of patients who were dependent or dead. These differences were significant.

4.4 Antihypertensive therapy
Systemic hypertension in the acute phase of ischemic stroke is common and is believed to be a physiologic response that maintains adequate cerebral perfusion to the ischemic penumbra [85]. While appropriate in primary and secondary stroke prevention, the lowering of elevated blood pressure (BP) in the acute setting has been a matter of debate for several years. Some studies have suggested that it could result in the extension and worsening of stroke symptoms, resulting in unfavorable outcome [86-88]. In contrast, other experimental and clinical studies demonstrated that a cautious reduction of BP may even improve the prognosis in acute cerebral ischemia [89,90]. The current recommendation to tolerate acute hypertension in cerebral ischemia is based on the concept of disturbed autoregulation of cerebral blood flow in the penumbra surrounding the zone of necrosis. However, the multicenter Phase II ACCESS (Acute Candesartan Cilexetil Therapy in Stroke Survivors) [91] study showed that candesartan in the acute phase of ischemic stroke was safe, with no cerebrovascular event occurring as a result of hypotension. Encouraged by the success of ACCESS, several studies dealing with antihypertensive drugs for acute ischemic stroke are ongoing, including COSSACS (Continue Or Stop post Stroke Antihypertensives Collaborative Study; to determine whether antihypertensive therapy should be continued in the acute situation), CHHIPS (Control of Hypertension and Hypotension Immediately Post Stroke; to determine the extent to which BP should be lowered in the acute stroke setting) and SCAST (Scandinavian Candesartan Acute Stroke Trial; to assess whether candesartan given to patients with elevated BP in the acute phase of stroke reduces the cardiovascular risk).

4.5 Glucose management
Although diabetes and hyperglycemia are associated with worse outcomes in acute ischemic stroke, the glycemia levels to initiate treatment with insulin are arbitrary, and the efficacy and safety of aggressive glycemia control is unknown. The GIST-UK (United Kingdom Glucose Insulin in Stroke Trial) is a multicenter randomized trial that seeks to determine whether an infusion of glucose, insulin and potassium is favorable in acute stroke outcome.

4.6 Stroke units
Approximately one-third of stroke patients will suffer neurologic worsening during the first 48 h after the event [92]. Although it is difficult to predict which patients will deteriorate, hospital admission with proper vigilance might allow an early detection of worsening and facilitate an adequate medical response. A stroke unit is a geographically defined facility, which has the capability to permit close observation of changes in patients’ neurologic status. Several studies have demonstrated the use of comprehensive stroke units in lowering the rates of mortality and morbidity after stroke. Stroke unit care most often includes a coordinated multidisciplinary team, staffed by people with an interest in stroke, staff education programs, routine provision of information to patients and caregivers, and involvement of caregivers as well as technical and human resources for delivering stroke unit care. The typical components of care in the stroke unit trials were [93,94]: i) assessment (medical assessment and diagnosis including CT scanning, early assessment of nursing and therapy needs); ii) early management policies (early mobilization, prevention of complications, treatment of hypoxia, hyperglycemia, pyrexia and dehydration); and iii) ongoing rehabilitation policies.
A meta-analysis by the Stroke Unit Trialist’s Collaboration [95] showed an 18% relative reduction in mortality, a reduction in death or dependence, and a reduction in death or need of institutional care when treated in a stroke unit in comparison with a general medical ward. The absolute changes indicated a 3% reduction in all-cause mortality, a 3% reduction in the need for nursing home care and a 6% increase in the number of independent survivors. The beneficial effect is long standing for ≤ 5 – 10 years [96].

4.7 Cell therapy for stroke

Once the damage from a stroke has maximized, little can be done to recover premorbid function. Several novel neurorestorative approaches are being investigated as adjunctive treatments to physiotherapy. Experimental animal data support the safety and effectiveness of cell transplantation to enhance neurologic recovery from stroke. A variety of cells as implant sources have been investigated, including stem cells, immortalized cell lines, marrow and adipose stromal cells, and porcine fetal cells. Buoyed by the success of animal data, clinical trials have already commenced [97].

5. Conclusions

Stroke is a global health problem. It is the leading cause of adult disability and the second leading cause of mortality worldwide. Knowledge of acute ischemic stroke pathophysiology has improved widely in the last 25 years and, as a consequence, numerous new therapeutic strategies have been tested. The two fundamental strategies are: i) to minimize the deleterious effect of ischemia on neurons; and ii) to restore blood flow as soon as possible. In preclinical studies, many drugs have proved to be neuroprotective although most of them have failed in clinical trials. At present, there are no compounds approved for stroke neuroprotection therapy, but several promising agents are under checking. At 10 years after the FDA approval for medical use of intravenous alteplase in ischemic stroke, the reperfusion approach has recently taken a new impetus after the SITS-MOST results publication. Moreover, new perspectives are opened based on endovascular mechanical therapies. Meanwhile, stroke units have demonstrated clear benefits for patients and it is necessary to expand its implantation in most hospitals.

6. Expert opinion

After the NINDS rt-PA study publication, the classical, nihilistic approach to ischemic stroke started to change. However, > 10 years later, < 4% of patients receive treatment with alteplase. Moreover, intravenous thrombolysis has many limitations, including: i) its unavailability to treat patients after 3 h of stroke onset; ii) the fact that reperfusion and complete functional recovery is achieved by < 40% of patients; iii) symptomatic hemorrhagic transformations are still high [5%]; and iv) there are no broadly accepted alternatives for non-responders. Therefore, neurologists are currently involved in new investigations to fight against these limitations. It is probable that sonothrombolysis, intra-arterial thrombolysis and endovascular devices could increase the rate of recanalization in the near future. In our opinion, in spite of the development of new drugs capable of prolonging the efficacy and improving the safety of clot lysis, reperfusion therapy in ischemic stroke in the following years will shift from a pharmaceutical thrombolysis to a mechanic one where endovascular devices and acute angioplasty will have a prominent role, as has occurred in acute coronary syndrome management. However, the paramount advance in acute stroke therapy will be the use of multi-modal imaging techniques and serum biomarkers to predict with reasonable accuracy the location and amount of irreversible ischemic damage. This fact will change the idea of a general timing clock in thrombolysis to an individualized tissue clock in ischemic stroke. Of course, this tissue clock will have to be influenced not only by time or the individual idiosyncratic response to ischemic insult, but also by the neuroprotective therapy that neurologists might offer to our patients. In the next years, medicine will have to find an effective neuroprotection with the ability to prolong the temporal window of the tissue clock. It will probably be necessary to improve our current methodology for investigations, assuming the STAIR recommendations. Moreover, effective neuroprotection will require investigators to identify valid strategies to protect not only neurons, but also vascular and glial cells. To avoid previous fails, the most efficient approach might be a polytherapy one that combines drugs with different mechanisms of action. Ideally, these drugs will be safe, well tolerated and effective in a broad range of patients including those who suffer hemorrhagic stroke, and will give us the opportunity for an immediate–even paramedic–administration soon after event onset, without any delay due to the requirement for selection by a CT scan.

Finally, we think that the following 10 years will see the growth of the neuro-reparation therapy in stroke management. Based on advances in stem cell biology and genomics, there will be a great potential to regenerate and replace neurons that have died. At present, this knowledge is only beginning in cerebrovascular diseases and important issues will have to be explored before this therapy could be offered to our patients. In addition, we are sure that the coming years will be an exciting time to work within the area of and improve on acute ischemic stroke management.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.
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