HYPERACUTE MANAGEMENT OF ISCHEMIC CEREBROVASCULAR STROKE

Essay
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INDEX

Pathophysiology of stroke.................................................................3
Neuro-imaging in stroke.................................................................17
Hypercute management of ischemic stroke.....................................25
Thrombolysis in ischemic stroke.....................................................27
Intravenous thrombolysis with rt-PA.............................................33
Intra-arterial thrombolysis............................................................52
Intra-arterial chemical thrombolysis ............................................56
Intra-arterial mechanical thrombolysis .........................................61
Neuroprotection...........................................................................70
Management of hypertension.........................................................82
Management of ischemic cerebral edema........................................85
Recommendations..........................................................................92
Algorithm for hyperacute stroke management..............................98

References......................................................................................99
Pathophysiology Of Stroke

Advances in understanding the pathophysiology and evolution of ischemic brain injury are the obvious rational basis for the development of therapy for acute ischemic stroke \cite{Cheng et al.2004}. The current understanding of pathophysiology has dramatically evolved over the past three decades, from early beginnings in animal studies to the current wealth of information provided by various imaging techniques \cite{Saver, 2006}.

Definition And Classification

A stroke is the rapidly developing loss of brain function(s) due to disturbance in the blood supply to the brain. This can be due to ischemia caused by thrombosis or embolism or due to a hemorrhage. As a result, the affected area of the brain is unable to function \cite{Donnan et al.,2008}.

Ischemia is due to interruption of the blood supply, while hemorrhage is due to rupture of a blood vessel or an abnormal vascular structure. 80% of strokes are due to ischemia; the remainder are due to hemorrhage. Some hemorrhages develop inside areas of ischemia ("hemorrhagic transformation"). It is unknown how many hemorrhages actually start off as ischemic stroke \cite{Donnan et al.,2008}.

There are various classification systems for acute ischemic stroke. The TOAST classification is based on clinical symptoms as well as results of further investigations; on this basis, a stroke is classified as being due to (1) thrombosis or embolism due to atherosclerosis of a large artery, (2)
embolism of cardiac origin, (3) occlusion of a small blood vessel, (4)
other determined cause, (5) undetermined cause. (Donnan et al., 2008).

The most common subtypes of ischemic stroke are atherosclerosis (large vessel), cardioembolic, and lacunar (small vessel). The exact percentages of each subtype vary depending on race, ethnicity, age, and sex (Baumgartner et al., 2003).

The atherosclerosis, or large vessel stroke, is defined as a greater than 50% stenosis of the carotid, middle cerebral, anterior cerebral, posterior cerebral, basilar, or vertebral arteries. This subtype carries the greatest chance of causing significant clinical deterioration (Albers et al., 2001).

A cardioembolic stroke is defined as one in which cardiac conditions, such as myocardial infarction within 6 weeks of stroke onset, congestive heart failure, mitral stenosis, artificial heart valve, atrial fibrillation or flutter, or thrombus present in the ventricle, are present contributing to the formation of a clot and potential embolism (Schneider et al., 2004).

Small vessel stroke, or lacunar stroke, is a small ischemic lesion occurring deep in the cortical tissue, with traditional clinical syndromes and no potential large vessel or cardiac causes (Baumgartner et al., 2003).

A more specific definition divides lacunar stroke into 3 conditions. Condition A is a deep infarct of 1.5 cm in diameter and is accompanied by clinical symptoms. Condition B reveals no brain images representing an infarct, yet the patient demonstrates clinical symptoms of a stroke. Condition C occurs when the scan shows a 1.5 cm deep infarct with a clinical syndrome that is not one of the classical syndromes of lacunar stroke (Schneider et al., 2004). Lacunar strokes carry the best chance for recovery and survival (Albers et al., 2001).
Stroke without an obvious explanation is termed "cryptogenic" (of unknown origin); this constitutes 15-20% of all ischemic strokes (Donnan et al., 2008).

**Ischemic Penumbra**

The penumbra concept of focal ischemia is of considerable interest for the understanding of stroke pathophysiology because it is the conceptual basis not only for the progressive evolution of ischemic injury, but also for the therapeutic reversal of the acute neurological symptomatology arising from stroke (Fisher, 2004).

The brain’s response to acute ischemia is influenced by the severity and duration of the insult. Experimental stroke models suggest that there are different ischemic thresholds for cerebral dysfunction and cell death. Normal cerebral blood flow is approximately 50 to 55 mL/100 g/min. When blood flow drops to about 18 mL/100 g/min, the brain has reached the threshold for synaptic transmission failure. Although these cells are not functioning normally, they do have the potential for recovery. The second level, known as the threshold for membrane pump failure, occurs when blood flow drops to about 8 mL/100 g/min. Cell death can result. The difference between these two blood flow levels (8 to 18 mL/100 g/min) has led to the concept of a perifocal ischemic region, or ischemic penumbra, in which there is loss of the EEG and flat evoked potentials but normal ATP and extracellular concentrations of k+ (Metwally, 2010).

Ischemic penumbra is usually peripheral in location, where blood flow is sufficiently reduced to cause hypoxia, severe enough to arrest physiological function, but not so complete as to cause irreversible failure of energy metabolism and cellular necrosis (Ginsberg, 2003).
Ischemic penumbra is a dynamic process. It exists for a short period of time even in the center of ischemia, where irreversible necrosis propagates to the neighboring tissue over time. It is very short for the core of ischemia and may extend to several hours in the moderately ischemic surrounding tissue (Heiss, 2000).

To better understand the ischemic penumbra, it is worthwhile to review the pathophysiologic mechanism of ischemic brain damage. Reviewing the “four tissue compartments concept” is a very good strategy for understanding the ischemic process. The compartments can be distinguished by the various physiological imaging modalities during acute ischemic stroke: 1) the unaffected tissue; 2) the mildly hypoperfused tissue, but this is not usually at risk (the oligemic tissue); 3) the tissue at risk (the ischemic penumbra); and 4) the tissue already irreversibly damaged (the ischemic core) (Baron, 2001).

The major concern during the initial hemodynamic evaluation of the acute ischemic patient is the viability of the penumbra zone. The degree of perfusion abnormality and the duration of the ischemia should be considered when predicting the fate of the total lesion. However, in clinical settings, predicting the viability of the penumbra zone is a complex task. Warach proposed “The 4-factor model” for this purpose. The model consisted of a time factor, a hemodynamic factor, a tissue factor and an intervention factor. There is no absolute viability threshold that is independent of time, and there is no absolute time window for the tissue viability (Warach, 2001).

Studies of brain injury have shown that focal cerebral ischaemia initiates a series of pathological events, where cells in the penumbra are subjected to various pathological processes leading to their own and their neighbours’ death. The molecular consequences of brain ischaemia
include temporal changes in cell signalling, signal transduction, metabolism, and gene regulation /expression (Slevin et al., 2005).

**Molecular Mechanisms of Injury Progression**

In the border zone of permanent focal ischemia or in the central part transient vascular occlusion, cellular disturbances may evolve that cannot be explained by a lasting impairment of blood flow or energy metabolism. These disturbances are referred to as molecular injury. The molecular injury cascades are interconnected in complex ways, which makes it difficult to predict their relative pathogenic importance in different ischemia models. In particular, molecular injury induced by transient focal ischemia is not equivalent to the alterations that occur in the penumbra of permanent ischemia. The relative contribution of the following injury mechanisms differ therefore in different types of ischemia (Nicotera, 2003).

Mechanisms of ischemic injury include edema, microvascular thrombosis, programmed cell death, and infarction with cell necrosis. Inflammatory mediators contribute to edema and microvascular thrombosis. Edema, if severe or extensive, can increase intracranial pressure. Many factors may contribute to necrotic cell death; they include loss of ATP stores, loss of ionic homeostasis, lipid peroxidative damage to cell membranes by free radicals, excitatory neurotoxins, and intracellular acidosis due to accumulation of lactate (Metwally, 2010).

**Ischemic Cascade**

The ischemic cascade induced by focal brain ischemia is complex and many additional components were discovered only recently (Chong et al., 2005).
If the flow is not reestablished in the blocked vessel, a series of destructive mechanisms or ischemic cascade occurs, leading to the cell death in the area of blood flow disruption. Ion channel disruption also occurs with an increase in calcium influx into the cell. Excitatory amino acids, glutamate and aspartate, are released. As these destructive agents act in the ischemic neuronal bed of cells, there is production of arachidonic acid, oxygen free radicals, nitric oxide, and eicosanoids. The end result is cerebral edema, cell damage, and neuronal cell death (Lindsbert, 2004).

**Excitotoxicity**

Glutamate mediates excitotoxic synaptic transmission via activation of N-methyl-D-aspartate (NMDA), Amino-3-hydroxy-5-methyl-4-propionate (AMPA) or kainate receptors. When glutamate is released from presynaptic terminals, it allows Na⁺ and Ca²⁺ influx that depolarizes the membrane. While this is vital for neuronal plasticity, additional activation of receptors results in neuronal death. Glutamate is released in an uncontrolled manner in ischaemic areas. The glutamate-calcium cascade induces a necrotic lesion and Ca²⁺-mediated excitotoxicity plays an important role in brain infarction (Mitsios et al., 2006)

NMDA receptors are highly permeable to Ca²⁺, Na⁺, K⁺ and H⁺ cations. Their activation is a primary cause of neuronal death after ischaemia that is accompanied by temporary elevation of extracellular glutamate. Ca²⁺ influx mediates NMDA neurotoxicity while Na⁺ influx contributes to swelling of neuronal cell bodies. Normally the free Ca²⁺ concentration in the cytoplasm is approximately 1/10,000 of its extracellular concentration. The export of Ca²⁺ from neurons into the extracellular environment occurs via processes that are linked to energy
utilization. Energy failure in the brain during hypoxia results in a passive efflux of K+ from cells, enhancing Ca2+ entry and release into neurons. The unregulated rise in intracellular cytoplasmic Ca2+ links glutamate excitotoxicity to biochemical processes resulting in further injury, i.e. oxidative stress (Mitsios et al., 2006).

**Oxidative stress**

Plenty of reactive oxygen species are generated during an acute ischemic stroke and there is considerable evidence that oxidative stress is an important mediator of tissue injury in acute ischemic stroke. After ischemic brain injury, the production of reactive oxygen species (ROS) may increase leading to tissue damage via several different cellular molecular pathways. Radicals can cause damage to cardinal cellular components such as lipids, proteins, and nucleic acids leading to subsequent cell death by modes of necrosis or apoptosis. The damage can become more widespread due to weakened cellular antioxidant defense systems. Moreover, acute brain injury increases the levels of excitotoxic amino acids which also produce ROS, thereby promoting parenchymatous destruction. (Valko et al., 2007).

The increase in oxygen free radicals triggers the expression of a number of pro-inflammatory genes by inducing the synthesis of transcription factors, hypoxia inducible factor 1, interferon regulator factor 1 and STAT3. As a result, cytokines are upregulated in the cerebral tissue and consequently, the expression of adhesion molecules on the endothelial cell surface is induced, including intercellular adhesion molecule 1 (ICAM-1), P-selectin and E-selectin which mediate adhesion of leukocytes to endothelia in the periphery of the infarct (Yilmaz and Granger, 2008).

**Inflammation**
Brain infarcts evoke a strong inflammatory response which is thought to contribute to the progression of ischemic brain injury. Both focal and global brain ischemia is associated with expression of a number of inflammatory cytokines and chemokines, while upregulation of adhesion molecules induces leukocyte recruitment to the vascular endothelium which may affect the survival of damaged neurons (Mitsios et al., 2006).

The most studied cytokines related to inflammation in acute ischemic stroke are tumor necrosis factor-α (TNF-α), the interleukins (IL), IL-1β, IL-6, IL-20, IL-10 and transforming growth factor (TGF)-β. While IL-1β and TNF-α, appear to exacerbate cerebral injury, TGF-β and IL-10 may be neuroprotective (Lakhan et al., 2009).

IL-1 has been implicated strongly in the pathogenesis of ischaemic brain damage, and the major form contributing to ischaemic injury is IL-1β rather than IL-1α. Elevated IL-1β mRNA expression occurs within the first 15-30 min after permanent middle cerebral artery occlusion and elevated IL-1β protein expression occurs a few hours later and remains elevated for up to 4 days (Caso et al., 2007).

Tumor necrosis factor-α is a major player in many neurodegenerative diseases including stroke, its main source being activated microglia. Tumor necrosis factor-α influences cell survival through the action on two different receptor subtypes, TNF-R1 and TNF-R2. TNF-R1 contributes to neuronal death, whereas TNF-R2 can be neuroprotective (Marchetti et al., 2004).

IL-10 gene expression is elevated in association with most major diseases in the CNS and aids survival of neurons and glial cells by blocking the effects of pro-inflammatory cytokines and promoting expression of cell survival signals. Moreover, patients with low plasma levels of IL-10 during the first hours after stroke were three times more
likely to have worsening neurological symptoms within 48 hours following the stroke (*Mitsios et al., 2006*).

There is increasing evidence that cellular adhesion molecules play an important role in the pathophysiology of acute ischemic stroke (*Yilmaz and Granger, 2008*). Soluble intercellular adhesion molecule-1 levels were significantly higher in patients who died compared to those who survived (*Rallidis et al., 2009*).

Within minutes of ischaemia, proinflammatory genes are upregulated and adhesion molecules are expressed on the vascular endothelium. Neutrophils then migrate from the blood into the brain parenchyma within hours after reperfusion, followed by macrophages and monocytes within a few days. The vast majority of macrophages in the infarct area appear to be derived from local microglia that are activated before macrophage infiltration from the blood (*Schilling et al., 2003*).

**Apoptosis**

Apoptotic cell death, also known as programmed cell death occurs in areas that are not severely affected by the injury. After ischemia, there is necrotic cell death in the core of the lesion, where hypoxia is most severe, and apoptosis occurs in the penumbra, where collateral blood flow reduces the degree of hypoxia (*Charriaut et al., 1996*).

In apoptosis, a biochemical cascade activates proteases that destroy molecules that are required for cell survival and others that mediate a program of cell suicide. During the process, the cytoplasm condenses, mitochondria and ribosomes aggregate, the nucleus condenses, and chromatin aggregates. After its death, the cell fragments into "apoptotic bodies," and chromosomal DNA is enzymatically cleaved to internucleosomal fragments (*Hengartner, 2000*).
Following stroke, there is an early response in gene expression of molecules such as the Bcl-2 family and p53. Then there is a release of proapoptotic molecules such as cytochrome c and apoptosis-inducing factor from mitochondria, leading to activation of caspases and other genes that augment cell death (Mitsios et al., 2006).

The major executioners in the apoptotic program are proteases known as caspases. Caspases exist as latent precursors, which, when activated, initiate the death program by destroying key components of the cellular infrastructure and activating factors that mediate damage to the cells. Procaspases are composed of p10 and p20 subunits and an N-terminal recruitment domain. Active caspases are heterotetramers consisting of two p10 and two p20 subunits derived from two pro-caspase molecules. Caspases have been categorized into upstream initiators and downstream executioners. Upstream caspases are activated by the cell-death signal (e.g., tumor necrosis factor) and have a long N-terminal prodomain that regulates their activation (Hengartner, 2000).

The caspase cascade can be activated by an extrinsic or death receptor-dependent route and an intrinsic (death receptor-independent) or mitochondrial pathway (Mitsios et al., 2006).

Neurons at the core of an ischaemic lesion undergo necrotic death and are resistant to caspase inhibitors, whereas neurons at the periphery show apoptotic features and can be partially rescued by caspase inhibitors (Mitsios et al., 2006).

The relevant contributions of both mechanisms of cell death (necrotic and programmed cell death) to the ultimate extent of infarction remain uncertain but are likely variable among individual patients. It remains probable that multiple mechanisms related to both pathways of cell death are activated simultaneously in individual patients, implying that multiple
components of the ischemic cascade need to be targeted to maximize tissue salvage (Fisher et al., 2003).

**Ischemia/reperfusion (I/R) injury**

The ischemic cascade usually goes on for hours but can last for days, even after restoration of blood circulation. Although reperfusion of ischemic brain tissue is critical for restoring normal function, it can paradoxically result in secondary damage, called ischemia/reperfusion injury. The definitive pathophysiology regarding I/R injury still remains obscure; however, oxidative stress mediators such as reactive oxygen species (ROS) released by inflammatory cells around the I/R injured areas are suggested to play a critical role (Wong and Crack, 2008).

In addition to direct cell damage, regional brain I/R induces an inflammatory response involving complement activation and generation of active fragments such as C3a and C5a anaphylatoxins. Expression of C3a and complement 5a receptors was found to be significantly increased after middle cerebral artery occlusion in the mouse indicating an active role of the complement system in cerebral ischemic injury. Complement inhibition resulted in neuroprotection in animal models of stroke (Arumugam et al., 2009).

**Molecular Mechanisms of Ischemic Cerebral Edema**

Cerebral edema is an excess accumulation of water in the intracellular and/or extracellular spaces of the brain. Classic dogma has stressed the importance of mechanical disruption of the blood-brain barrier and the resulting formation of vasogenic edema fluid in the development of cerebral edema following ischemic brain injury. Recent data has challenged this concept. Another paradigm holds that the development of cerebral edema is a complex yet stepwise process that stems first from
the cytotoxic edema of neuroglial cells (which does not require active blood flow) to the subsequent development of ionic and vasogenic edema (which occur once ischemic tissues are reperfused) (Simard et al., 2007).

Cytotoxic edema:

Cytotoxic edema is pathological cell swelling due to disruptions in cell volume regulation. It is the initial, and to some extent the predominant, type of edema following cerebral ischemia (Unterberg et al., 2004).

Cytotoxic edema promotes the intracellular accumulation of osmotically active solutes that not only cause cell swelling but also lead to the alteration of ionic gradients that promote the transendothelial passage of fluid into the extracellular space. Because astrocytes outnumber neurons 20 to 1 in humans, the uptake of solute into astrocytes is primarily responsible for cytotoxic edema (Kahle et al., 2009).

The primary driver behind the formation of cytotoxic edema is the intracellular accumulation of sodium. This ion is usually more highly concentrated in the extracellular space than in the intracellular space due to the selective permeability of the plasma membrane and the activity of the Na+-K+-ATPase. However, ischemia triggers changes in the cell membrane that render it more permeable to the passage of sodium. Chloride follows the influx of sodium through chloride channels, and water follows via aquaporin water channels to maintain electrical and osmotic neutrality, respectively (Kahle et al., 2009).

Excitatory amino acids like glutamate play a particularly important role in ischemic cell injury not only by triggering the excitotoxicity of neurons but also by stimulating the inward fluxes of sodium and chloride that promote cytotoxic brain cell swelling. After 30 min of ischemia, extracellular glutamate levels are increased by >150-fold due to impaired clearance. These high levels of glutamate produce neuronal and glial
injury and death in part by triggering an influx of sodium, chloride, and water, resulting in extensive cell swelling *(Kahle et al., 2009).*

**Ionic and vasogenic edema**

Cytotoxic edema of brain cells does not by itself increase the net volume of the brain unless cerebral blood flow is reestablished, because cytotoxic edema is the redistribution of fluid from the brain’s extracellular to intracellular space. For an actual increase in brain volume to occur, additional fluid must be added to the brain’s extracellular space. The movement of ions and water into cells from cytotoxic edema results in the depletion of these constituents from the extracellular space *(Stiefel and Marmarou, 2002).*

Newly established gradients for sodium and other osmotically active solutes between the intravascular space and the extracellular space are the driving forces for the transendothelial movement of edema fluid across the blood-brain barrier. However, the stored potential energy of these ionic gradients cannot manifest into solute and water movement until the permeability of cerebral endothelial cells of the blood-brain barrier is altered. Increased permeability of endothelial cells for sodium, chloride, and water, achieved by either increasing the expression of transcellular ion channels and transporters and aquaporin water channels (resulting in ionic edema), or the opening of tight junctions between endothelial cells (resulting in vasogenic edema) permits the flux of solute and water down their concentration gradients *(Kahle et al., 2009).*

Ionic edema is the earliest phase of endothelial dysfunction triggered by ischemia and precedes vasogenic edema. Increased permeability of endothelial cells is usually due to the increased activity and/or expression of ion transport proteins triggered by ischemia or associated toxic metabolites. Ionic edema fluid is protein poor because tight junctions of
the blood-brain barrier are intact. Because endothelial cells, unlike neurons and astrocytes, do not express voltage-gated sodium channels, the secondary active cotransporter NKCC1, expressed on the luminal side of the endothelium, plays an important role in the formation of ionic edema by loading sodium and chloride into cells. The sodium inside capillary cells is then expelled into the brain’s extracellular space by the activity of the Na+-K+-ATPase, which is expressed on the capillary cell adluminal membrane; chloride follows through anionic channels (Kahle et al., 2009).

After ionic edema, the second phase of endothelial dysfunction triggered by ischemia is vasogenic edema, which is characterized by the breakdown of tight junctions within the blood-brain barrier and an accumulation of fluid into the brain’s interstitial space. It is unclear what causes the permeability changes during vasogenic edema. Although the newly created permeability pores are large enough to permit the passage of plasma-derived macromolecules, the pores do not allow the passage of red blood cells, suggesting that physical disruption of capillaries is not the primary mechanism involved. Endothelial cell swelling due to cytotoxic edema, actin polymerization dependent endothelial cell retraction, formation of interendothelial gaps, tight junction breakdown, and enzymatic degradation of endothelial cell basement membranes are all mechanisms that have been proposed to account for changes in endothelial permeability accompanying vasogenic edema (Kahle et al., 2009).

Vasogenic edema also results when the capillary basement membrane is breeched via ischemia-induced matrix metalloproteinases; matrix metalloproteinase inhibitors reduce ischemia-induced or reperfusion associated cerebral edema (Fukuda et al., 2004).
Neuro-imaging In Stroke

Several authors have reported that computerized tomography (CT) and magnetic resonance imaging (MRI) can provide important data on the pathophysiology of cerebral ischemia as well as structural and functional information on potentially salvageable tissue (Linfante et al., 2004).

Computed tomography

The use of computed tomography for stroke evaluation has progressively increased, since magnetic resonance imaging is less widely available than CT outside major stroke centers and is much more limited by patient contraindications or intolerance (Tomandl et al., 2003). In recent years, the amount of information provided by the radiologist has increased owing to the use of additional CT techniques such as perfusion CT and CT angiography. Multimodal CT evaluation that combines nonenhanced CT, perfusion CT, and CT angiography has been shown to improve detection of acute infarction (Wintermark et al., 2006), permit assessment of the site of vascular occlusion, the infarct core, and salvageable brain tissue; and help assess the degree of collateral circulation (Tan et al., 2007). This multimodal approach requires only 10–15 minutes more than nonenhanced CT alone (Parsons et al., 2005).

The complete CT protocol, which includes nonenhanced CT, perfusion CT, and CT angiography, can be performed as a single examination with separate contrast material bolus. The examination is frequently completed and analyzed within 15 minutes in a real clinical setting using new-generation multidetector CT scanners. In addition, correlation of all the imaging findings with the vascular anatomy and clinical findings is crucial, since the latter two elements are linked and are necessary to
fulfill all the requirements for hyperacute stroke imaging \((Kloska \ et \ al.,2004)\).

**Nonenhanced CT**

Nonenhanced scanning must be performed as soon as possible when stroke is suspected as CT is highly sensitive for the depiction of hemorrhagic lesions \((Kucinski, 2005)\).

The second role of nonenhanced CT is the detection of ischemic signs of established infarction. The main CT finding is a cortical-subcortical hypoattenuating area within a vascular territory. Careful attention to the extent of the hypoattenuating area is crucial: The presence of hypoattenuation affecting more than one-third of the middle cerebral artery territory is a contraindication for revascularization because it has been demonstrated that hemorrhagic complications are associated with larger established infarcted lesions before treatment \((Tanne \ et \ al.,2002)\).

It is, however, well-known that nonenhanced CT has a relatively low sensitivity in the first 24 hours, especially within the limited time window for thrombolytic treatment \((Srinivasan \ et \ al.,2006)\).

In a review by Wardlaw and Mielke, a higher sensitivity (61\%) was observed for depiction of subtle early signs of infarction and ischemia, including \((a)\) subtle hypoattenuation, \((b)\) obscuration and loss of gray matter–white matter differentiation in the basal ganglia, \((c)\) cortical sulcal effacement, \((d)\) loss of the insular ribbon, and \((e)\) hyperattenuation of a large vessel (“hyper-attenuating MCA sign” or “dot sign” in an M2 branch). These signs are associated with a worse prognosis and poorer functional outcome \((Wardlaw \ and \ Mielke, 2005)\).
**Perfusion CT (PCT)**

Brain perfusion data play an important role in the pathologic assessment of patients with ischemic cerebrovascular disease and in therapeutic planning. In patients with acute stroke, perfusion studies may help physicians identify the penumbra zone and the hypoperfused brain tissue at risk of infarction (*Murphy et al., 2006*), and they may be used to obtain essential information to plan reperfusion therapy (*Schaefer et al., 2006*).

PCT is acquired using sequential imaging in cine mode after intravenous injection of an iodinated contrast medium (*Wintermark et al., 2005*).

PCT permits more accurate assessment of the infarct core than does unenhanced CT especially those for whom MR imaging cannot be obtained (*Wintermark et al., 2006*). PCT is significantly more sensitive and accurate and has a better negative predictive value than does unenhanced CT in the detection of acute brain ischemia within 3 hours of symptom onset (*Lin et al., 2009*).

PCT detectes abnormalities consistent with stroke/transient ischemic attack in many patients (32%) for whom no occlusion was identified on CTA; negative PCT/CTA predicted good outcome in most patients (*Tong et al., 2008*).

With the current PCT method, the dynamic perfusion status of the brain can be evaluated in a 0.5 sec time resolution and it can cover with a 20-30 mm slice thickness at a time. We can get each time-density curve on a pixel-by-pixel basis. Using these curves, several parameter maps can be reproduced, such as the time-to-peak (TTP) map, the mean transit time (MTT) map, the CBF map and the CBV map. It is believed that PCT is capable of providing quantitative data on both the CBF and the CBV,
unlike the current MR perfusion techniques (Wintermark and Bogousslavsky, 2003).

The ischemic tissue (penumbra) shows increased MTT with decreased CBF and normal or mildly increased CBV (secondary to autoregulatory mechanisms in the early stage of ischemia), whereas infarcted tissue shows markedly decreased CBF and increased MTT with markedly decreased CBV (Wintermark et al., 2007).

CT Angiography

CTA has demonstrated to be accurate in the evaluation of cervical and large-vessel intracranial occlusion and may be valuable to help triage acute stroke patients for intra-arterial fibrinolysis (Sims et al., 2005).

The branches of the contributing vessels can be evaluated based on a simplified version of the classic angiographic grading scale for collateral circulation: 0 = no visible collateral vessels to the ischemic site, 1 = visible collateral vessels to the periphery of the ischemic site, 2 = complete irrigation of the ischemic bed by collateral flow, and 3 = normal antegrade flow (Kim et al., 2004).

CT angiography is especially important for the detection of thrombosis of the vertebrobasilar system, since this entity is very difficult to detect at nonenhanced CT and the brainstem is frequently not included in the perfusion coverage (Sylaja et al., 2008).

Magnetic resonance imaging

With the advent of advanced MRI such as diffusion- (DWI) and perfusion-weighted imaging (PWI), the concept of using imaging criteria as opposed to strict time limits to identify patients likely to benefit from
thrombolysis has demonstrated growing promise. Multiple studies have demonstrated that intravenous thrombolysis can be safely and effectively given beyond the 3-hour window when patients are selected based on a perfusion–diffusion mismatch on MRI (Schellinger et al., 2007).

MRI can provide information on tissue status (diffusion-restriction and hemodynamic compromise), anatomical aspects (integrity of the blood-brain barrier and the site of vascular occlusion), and metabolic conditions (oxygen extraction and cerebral metabolic rate of oxygen), which allows the tailored application of recanalization therapy. These techniques could expand the current narrow therapeutic window for acute stroke therapy, and enable more patients to be candidates for recanalization strategies (Molina and Saver, 2005).

**Diffusion-weighted imaging (DWI)**

DWI is an advanced MRI technique that is able to detect water diffusion in brain tissue (Engelter et al., 2008).

The infarct pattern on DWI is correlated with the pathogenic mechanisms underlying the stroke and may predict stroke recurrence and outcome (Bang et al., 2005). Small acute lesions in multiple vascular beds on DWI provide insight into the stroke mechanism by predicting the proximal source of the embolism (Kimura et al., 2001). In addition, the apparent diffusion coefficient (ADC) may be useful for estimating the lesion age and distinguishing acute from subacute DWI lesions (Lansberg et al., 2001). Acute ischemic lesions can be divided into hyperacute lesions (low ADC and DWI-positive) and subacute lesions (normalized ADC). Chronic lesions can be differentiated from acute lesions by normalization of ADC and DWI. The presence of multiple DWI lesions of varying ages suggests active early recurrences over time.
and portends a higher early risk of future ischemic events (Sylaja et al., 2007).

Perfusion-weighted imaging (PWI)

Perfusion-weighted MRI are currently acquired using the dynamic-susceptibility contrast imaging technique. This is very similar to the computed tomography perfusion technique. A series of susceptibility-weighted images (known as T2*) are obtained every 1-2 sec during an injection of intravenous gadolinium contrast. As contrast transits the cerebral circulation, MRI T2* signal intensity of the images successively decreases due to the paramagnetic nature of the contrast, and then returns to normal. This change in signal intensity is plotted as a function of time (the signal-intensity time curve). The central volume principle is used to calculate cerebral blood flow (CBF) and cerebral blood volume (CBV) on a voxel-wise basis. CBF is proportional to the amplitude of the signal intensity time curve, while CBV is estimated from the area under the signal-intensity time curve (Ostergaard, 2005). Areas of hypoperfusion can also be visualized as tissue with delayed time to peak (TTP) or prolonged mean transit time (MTT). Although not always performed in real time, most PWI studies have also used the deconvolution technique to correct for delay and dispersion of contrast bolus prior to arrival in the brain (Calamante et al., 2002). A commonly used parameter in these studies is Tmax, which is simply the time to peak after deconvolution of the signal-intensity time curve. Voxel-wise values for each parameter are assigned a color code or intensity value, and maps are then constructed for CBF, CBV, TTP, Tmax and MTT (Butcher et al., 2005).
Diffusion-perfusion mismatch

Animal and human studies have demonstrated that diffusion weighted imaging (DWI) combined with perfusion weighted imaging (PWI) sequences including regional cerebral blood volume (rCBV), relative CBF (rCBF), and mean transit time (MTT) maps can accurately represent the ischemic penumbra and predict the final size of the infarct (Feng et al., 2003).

The protons on water molecules in ischemic areas have restricted diffusion and will generate hyperintense signals and display a correspondent signal drop on the apparent diffusion coefficient maps. Hyperintense lesions on DWI are considered the MR equivalent of the infarction core, whereas the mismatch between the DWI abnormal signal and perfusion deficit on PWI represents the ischemic penumbra. DWI and PWI enable the diagnosis of small vessel stroke (lacunes). Patients with lacunar strokes can have severe deficits that mimic large-vessel occlusions but are caused by small-vessel occlusions. MRI techniques can help guide the use of intravenous thrombolytic and mechanical revascularization techniques (Tatlisumak et al., 2004).

Magnetic resonance angiography (MRA)

Magnetic resonance angiography (MRA) can be performed using the time of flight (TOF), repetitive pulses are used to saturate tissue, while mobile protons in the vessels create a signal that is utilized to create images of the vasculature. Areas with turbulent flow, slow flow and adjacent fat or blood products can lead to erroneous estimation of vessel lumen diameter and patency (Zsarlak et al., 2004).
Contrast-enhanced (CE) MRA utilizes gadolinium as an intravascular contrast medium. CE-MRA has a higher signal-to-noise ratio compared to conventional MRA, and visualization of smaller intracranial vessels (beyond the proximal middle cerebral artery) is improved (Sohn et al., 2003).

MRA has a satisfactory sensitivity and specificity (80-90%), as compared to intra-arterial angiography, for detection of high-grade stenosis or occlusion of the internal carotid (ICA). For moderately severe ICA stenosis and for assessment of intracranial vessels, the sensitivity is less than optimal (0-18% for intracranial stenosis ≥50%) (Debrey et al., 2008).
Hyperacute Management Of Ischemic Stroke

Hyperacute ischemic stroke management has rapidly evolved since the Food and Drug Administration approval of intravenous recombinant tissue plasminogen activator in 1996, which was based on the National Institute of Neurological Disorders and Stroke (NINDS)-supported acute stroke study. Different strategies for treating acute ischemic stroke have included primary intra-arterial therapy, as reported in several case series and the Prolyse in Acute Cerebral Thromboembolism (PROACT) trials, and combined IV/IA therapy, as seen in several other studies. Mechanical clot disruption techniques are also implemented with and without fibrinolytic therapy. Varying degrees of success have been demonstrated with these interventions (Wolfe et al., 2008).

There is a narrow window during which this can be accomplished, since the benefit of thrombolysis decreases in a continuous fashion over time. Thus, an important aspect of the hyperacute phase of stroke assessment and management is the rapid determination of patients who are eligible for thrombolysis. Focusing on patient care areas and support services, The “patient care” topics identified 6 major interconnecting elements including:

(1) identification of the patient and rapid transport to a “stroke receiving hospital” by the Emergency Medical Services system,
(2) ED prioritization of stroke care with rapid triage, protocols for patient management, and procedures for rtPA administration,
(3) organized acute stroke team for rapid response to the ED,
(4) written care protocols for the multidisciplinary team to follow integrating evidence-based literature,
(5) designated stroke unit with staff highly skilled to deal with stroke patients, and
(6) neurosurgeons available within 2 hours in case there is a need for a neurosurgical procedure (Alberts et al., 2000).

Stabilization may need to precede complete evaluation. Comatose or obtunded patients may require airway support. If increased intracranial pressure is suspected, intracranial pressure monitoring may be necessary. Specific acute treatments vary by type of stroke. Providing supportive care, correcting coexisting abnormalities (eg, fever, hypoxia, dehydration, hyperglycemia, sometimes hypertension), and preventing and treating complications are vital during the acute phase and convalescence; these measures clearly improve clinical outcomes (Metwally, 2010).
Thrombolysis In Ischemic Stroke

The thrombous and the thrombolytic system

In the absence of injury the vascular endothelium is antithrombotic, resisting platelet adherence and providing an unfriendly surface for coagulation factor interaction. When vascular injury does occur, the explosive potential of endogenous hemostasis is unleashed with the rate of coagulation reactions enhanced nearly 300,000-fold. Platelets adhere to exposed subendothelium, and aggregation proceeds with layers of activated platelets then proving a user-friendly surface for the complex molecular interactions of the coagulation cascade. Fibrin is generated, and the clot grows and then gradually stabilizes. Over a period of hours, autolysis of the cellular elements occurs, and the initially single stranded fibrin chains undergo cross-linking. A mature thrombus results that over time becomes increasingly resistant to enzymatic degradation. In cerebral vascular disease, the morphology of pathologic thrombi is largely unknown even though thrombi are fundamental in the pathogenesis of acute ischemic stroke. Angiographic studies completed within 8 hours of symptom onset indicate an acute occlusive thrombus is present in 70% or more of the patients examined (Metwally, 2010).

Because thrombotic and embolic arterial occlusions are the leading causes of cerebral infarction, pharmacologic therapy directed at achieving acute cerebral arterial recanalization via thrombolysis is gaining widespread attention. The ideal thrombolytic agent should be nonantigenic, inexpensive, safe, and capable of dissolving thrombi selectively (Metwally, 2010).
**Plasminogen Activators.**

These drugs act by converting the inactive proenzyme, plasminogen, into the active enzyme, plasmin. Plasmin digests fibrinogen, fibrin monomers, and cross-linked fibrin into fibrin degradation products. The plasminogen activators vary in stability, half-life, and fibrin selectivity. In general, the nonfibrin-selective drug scan result in systemic hypofibrinogenemia, whereas the fibrin-selective agents are mostly active at the site of thrombosis (*Nogueira et al.,* 2009).

*First-generation agents.*

Streptokinase and urokinase, are nonfibrin selective and could therefore have greater systemic complications. Streptokinase, a protein derived from group C β-hemolytic streptococci, has a half-life of 16–90 minutes and low fibrin specificity (*Nogueira et al.,* 2009). This drug proved to have a very narrow therapeutic window and significant rates of ICH and systemic hemorrhage; thus, it is no longer used for ischemic stroke (*Cornu et al.,* 2000). Urokinase is a serine protease with a plasma half-life of 14 minutes and low fibrin specificity (*Lisboa et al.,* 2002).

*Second-generation agents.*

Alteplase (rtPA) is a serine protease with a plasma half-life of 3.5 minutes and a high degree of fibrin affinity and specificity (*Lisboa et al.,* 2002). The theoretic disadvantages of alteplase include its relatively short half life and limited penetration into the clot matrix because of strong binding with surface fibrin, which could delay recanalization and increase the risk of recurrent occlusion. Additionally, rtPA appears to have some neurotoxic properties, including activation of metalloproteinases, which may result in increased blood-brain barrier permeability leading to cerebral hemorrhage and edema and amplification
of calcium currents through the \( N \)-methyl D aspartate receptor, leading to excitotoxicity and neuronal death (Kaur et al., 2004).

**Prourokinase**

Prourokinase (r-prourokinase) is the proenzyme precursor of urokinase. It has a plasma half life of 7 minutes and high fibrin specificity (Nogueira et al., 2009).

**Third-generation agents**

Third-generation agents such as reteplase and tenecteplase, have longer half-lives and theoretically favorable vessel recanalization and local recurrence rates. Reteplase is a structurally modified form of alteplase, with a longer half-life (15 to 18 minutes). In addition, it does not bind as highly to fibrin; unbound reteplase can thus theoretically better penetrate the clot and potentially improve in vivo fibrinolytic activity (Nogueira et al., 2009).

Tenecteplase is another modified form of rtPA with a longer half-life (17 minutes), greater fibrin specificity, and greater resistance to plasminogen activator inhibitor-1 (Nogueira et al., 2009).

**New-generation agents**

**Desmoteplase**

Desmoteplase is a genetically engineered version of the clot-dissolving factor found in the saliva of the vampire bat *Desmodus rotundus*. This drug is more potent and more selective for fibrin-bound plasminogen than any other known plasminogen activator. Unlike tissue plasminogen activator, desmoteplase is not activated by fibrinogen or amyloid proteins, factors that may exacerbate the risk for ICH. Moreover,
desmoteplase inhibits tPA-induced potentiation of excitotoxic injury. However clinical trials showed bad results (Nogueira et al., 2009).

Alternatives to Plasminogen Activation:

New drugs that do not depend on the availability of plasminogen are being evaluated for stroke therapy.

Direct fibrinolytics. V10153 is a recombinant variant of human plasminogen, which has been genetically modified to be activated to plasmin by thrombin rather than by endogenous plasminogen activator enzymes, such as tissue-type plasminogen activator. Because thrombin activity is primarily localized at the site of new thrombus formation, administration of V10153 results in the selective production of plasmin at the site of newly formed clot. Consequently, thrombus dissolution may be achieved without systemic plasmin generation, which should result in a reduced risk of hemorrhage. The relatively long plasma half-life (3–4 hours) of V10153 allows bolus administration, and persistence in the circulation may prevent early vascular reocclusion (Nogueira et al., 2009).

Microplasmin is a truncated form of plasmin that is more resistant to the effects of antiplasmin. Treatment of Ischemic Stroke-IntraVenous (MITI-IV) trial, a phase II multicenter randomized double-blinded placebo-controlled ascending dose clinical trial, evaluated the safety and preliminary efficacy of IV microplasmin in 40 patients treated 4–12 hours after stroke onset. There was no evidence of increased bleeding risk with microplasmin. Reperfusion occurred in 25% of patients treated with microplasmin versus 10% of placebo-treated patients (Nogueira et al., 2009).

Alfimeprase is a recombinant form of fibrolase, a fibrinolytic zinc metalloproteinase isolated from the venom of the southern copperhead.
snake. It degrades fibrin directly and achieves thrombolysis independent of plasmin formation. Alfimeprase is rapidly inactivated by α-2 macroglobulin as it moves away from the site of delivery into blood circulation. Thus, its thrombolytic activity appears to be localized to the site of delivery. These properties should theoretically result in faster recanalization and lower hemorrhagic conversion risk. The initial data on the safety and efficacy of alfimeprase appeared promising. A phase II multicenter open-label dose-escalation study of alfimeprase in the treatment of acute ischemic stroke (CARNEROS-1) within 3–9 hours of stroke onset is planned (Nogueira et al., 2009).

Defibrinogenating/Fibrinogenolytic agents. Ancrod is the purified fraction of the Malayan pit viper venom. It acts by directly cleaving and inactivating fibrinogen and thus indirectly promoting anticoagulation. The reduction in the blood levels of fibrinogen also leads to a reduced blood viscosity, which may improve blood flow to the affected areas of the brain. In addition, ancrod promotes an indirect activation of the plasminogen-plasmin pathway (Nogueira et al., 2009).

In the Stroke Treatment with Ancrod Trial, 500 patients with stroke presenting within 3 hours of symptom onset were randomized to receive ancrod or a placebo. Good outcome was achieved in 42.21% and 34.4% of the patients respectively. There was no significant difference in mortality, but a trend toward more sICH with ancrod (Sherman et al., 2000).

Adjunctive therapy

Fibrinolytic agents have prothrombotic properties as well. The plasmin generated by thrombolysis leads to the production of thrombin, which is a potent platelet activator and converts fibrinogen to fibrin. Indeed, studies have shown early reocclusion in as many as 17% of the patients treated
with IAT and 34% of the patients treated with IV rtPA. Therefore, a strong rationale exists for the adjuvant use of antithrombotic agents (Nogueira et al., 2009).

Systemic anticoagulation with IV heparin after 24 hours of IAT has several potential advantages, including augmentation of the thrombolytic effect, prevention of acute reocclusion, and reduction in the risk of catheter related embolism. However, these benefits must be weighed against the potentially increased risk of ICH when heparin is combined with a thrombolytic agent (Nogueira et al., 2009).

The use of glycoprotein (GP) IIb/IIIa antagonists, such as ReoPro (abciximab), in ischemic stroke remains investigational. The CLEAR trial evaluated the combination of low dose IV rtPA (0.6 mg/kg) and eptifibatide in patients with NIHSS scores more than 5 who presented within 3 hours from stroke onset. The study showed that the combination of eptifibatide and reduced-dose rtPA was judged safe enough for consideration of further dose-ranging trials in acute ischemic stroke (Pancioli et al., 2008). ROSIE is another trial that is evaluating the use of IV reteplase in combination with abciximab for the treatment of MR imaging selected patients with stroke within 3–24 hours from onset. Preliminary analysis of the first 21 patients enrolled has revealed no sICH or major hemorrhage. Conversely, the AbESTT II trial, a study evaluating the safety and efficacy of abciximab in acute ischemic stroke treated within 6 hours after stroke onset was stopped early due to high rates of sICH or fatal ICH in the abciximab treated patients (Adams et al., 2008).
Intravenous rt-PA

The US Food and Drug Administration approved intravenous rt-PA as a treatment for acute ischemic stroke and this treatment is the only approved medical therapy for patients with acute ischemic stroke. It is recommended as first-line treatment by most national and international stroke associations (Adams et al., 2003).

Tissue-type plasminogen activator is a naturally occurring thrombolysis activator with a molecular weight of approximately 70 kilodaltons which is now available for clinical use as a result of recombinant DNA technology. Tissue-type plasminogen activator has several advantages as a thrombolytic agent: It has a functional half-life of about 5 minutes, compared to about 16 minutes for urokinase and 23 minutes for streptokinase; thus, if bleeding occurs or invasive procedures are needed, the thrombolytic action of the drug disappears shortly after the infusion is discontinued. It is clot-specific because of its high affinity for plasminogen in the presence of fibrin. This allows efficient activation of the fibrin clot without activation occurring in the plasma. It causes only a modest reduction in fibrinogen concentration compared with the reduction caused by streptokinase. It is nonantigenic and usually causes no adverse reactions other than bleeding (Metwally, 2010).

Structure

Tissue plasminogen activator (t-PA) is an endogenous human serine protease found in the intravascular space, in the blood–brain interface, and in the brain parenchyma (neurons, astrocytes, and microglia) (Siao et al., 2003).

T-PA is composed by five conserved domains (finger, epidermal growth factor-like, K1, K2, and catalytic domain) that are differently involved in the pleiotropic functions of the molecule (Yepes et al., 2009).
Mechanism of action

T-PA plays a central role in maintaining homeostatic control in the blood coagulation cascade. By cleaving the precursor molecule plasminogen, it produces the active enzyme plasmin, which then dissolves fibrin-based clots in focal cerebral ischemia. By contrast, in the brain parenchyma, t-PA has been associated with multiple physiologic and pathologic events including synaptic plasticity and cell death (Giuseppe et al., 2009). In pathologic conditions, t-PA has been linked to neurotoxicity especially cell injury induced by activation of excitatory amino acid receptors (Yepes and Lawrence, 2004).

Its functions may include facilitation of axon elongation (by degradation of the extracellular matrix) and long-term potentiation of memory (LPT). This effect seems to be related to potentiation of glutamate receptor signaling and, more specifically, to the ability to cleave the NR1 subunit of the NMDA receptor, resulting in enhanced Ca2+ influx into the neuron. Moreover, the degradation of the extracellular matrix by t-PA seems to have a role in the physiological effect of t-PA on LTP (Benchenane et al., 2004).

There is considerable release of endogenous t-PA in animal models of stroke, leading to incoordinate effects on NMDA receptor signaling and on the extracellular matrix. Thus, the physiologic effects of t-PA may become deleterious in the setting of cerebral ischemia (Benchenane et al., 2004).

Likewise, destructive effects on the extracellular matrix and the endothelial basal lamina would explain the finding that rt-PA can compromise the integrity of the blood–brain barrier and finally cause overt hemorrhage. also a central factor for the propensity of rt-PA to cause intracerebral hemorrhage may be its ability to cross the BBB by
virtue of its proteolytic activity, as observed in animal studies (Yepes and Lawrence, 2004).

Window of treatment

Administration of rt-PA within three hours of symptom onset is associated with a greater chance of a favorable outcome at three months. It is nearly twice as efficacious when administered within the first 1.5 hours after the onset of ischemic stroke as when administered within 1.5 to 3 hours after stroke onset (Hacke et al., 2004).

The recently published trial European Cooperative Acute Stroke Study III (ECASS III) has shown that intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improves clinical outcomes in patients with acute ischemic stroke compared to placebo. The number needed to treat, to get one more favourable outcome was two during the first 90 minutes, seven within 3 hours and 14 between 3 and 4.5 hours (Hacke et al., 2008).

In comparison with pooled analysis of previous randomized trials, in ECASS III, the odds ratio for a good outcome was 1.34 and the NNT for a good outcome is equal to 14. The effectiveness of alteplase in an extended time window up to 4.5 hours is confirmed by evaluation of the data from the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR) registry which shows that the rates of sICH, mortality, and independence at three-month followup in routine clinical practice are similar in patients who received treatment between three and 4.5 hours and for those treated within three hours from stroke onset (Micieli et al., 2009).

The SITS investigators compared 664 patients with ischaemic stroke treated between 3 and 4.5 hours with 11865 patients treated within 3 hours. There were no significant differences between the 3-4.5-hour
cohort and the 3-hour cohort for any outcome measures, confirming that alteplase remains safe when given between 3 and 4.5 hours after the onset of symptoms in ischaemic stroke patients (Wahlgren 2008).

**Indications for tPA (Adams et al.,2007)**

- Acute onset of focal neurological symptoms, consistent with ischemic stroke in patients 18 years of age and older.

- Clearly defined onset of stroke less than 4.5 hours prior to planned start of treatment (Hacke et al., 2004).

- Baseline NIHSS score ≥4 except dysphasia.

- CT scan does not show evidence of intracranial hemorrhage, non-vascular lesions (e.g., brain tumor, abscess) or signs of advanced cerebral infarction such as sulcal edema, hemispheric swelling, or large areas of low attenuation consistent with extensive volume of infarcted tissue.

- Patients with ≥20% PWI-DWI mismatch.

- A patient with a seizure at the time of onset of stroke may be eligible for treatment as long as the physician is convinced that residual impairments are secondary to stroke and not a postictal phenomenon.

**Contraindications for tPA (Adams et al.,2007)**

**Clinical contraindications**

- Clearly defined onset of stroke greater than 4.5 hours prior to planned start of treatment (Hacke et al., 2004).

- Rapidly improving symptoms.

- Mild stroke symptoms/signs
  - Sensory symptoms only.
- Ataxia without other deficits.
- Dysarthria without other deficits.
- Mild motor signs (non-disabling).
- Visual field defect without other deficits.

• Baseline NIHSS score ≤ 4 except dysphasia.

• In the setting of middle cerebral artery stroke, an obtunded or comatose state may be a relative contraindication.

• Clinical presentation suggestive of subarachnoid hemorrhage, regardless of CT result.

• Persistent hypertension – systolic blood pressure greater than 185 mmHg or diastolic blood pressure greater than 110 mmHg.

• Minor ischemic stroke within the last month.

• Major ischemic stroke or head trauma within the last three months.

• Past history of intracerebral or subarachnoid hemorrhage.

• Untreated cerebral aneurysm, arteriovenous malformation or brain tumor.

• Gastrointestinal or genitourinary hemorrhage within the last 21 days.

• Arterial puncture at a non-compressible site within the last seven days or lumbar puncture within the last three days.

• Major surgery or major trauma within the last 14 days.

• Clinical presentation suggestive of acute myocardial infarction (MI) or post-MI pericarditis.

• Patient taking oral anticoagulants and INR greater than 1.7.
• Patient receiving heparin within the last 48 hours and has an elevated aPTT.

• Patient receiving low-molecular-weight heparin within the last 24 hours.

• Pregnant, or anticipated pregnant, female.

• Known hereditary or acquired hemorrhagic diathesis or unsupported coagulation factor deficiency.

_Laboratory contraindications_

• Glucose less than 50 or greater than 400 mg/dL.

• Platelet count less than 100,000/mm³.

• INR greater than 1.7.

• Elevated aPTT.

• Positive pregnancy test.

_Radiology contraindications_

• Intracranial hemorrhage.

• Large area of low attenuation consistent with an infarcted brain.

• Intracranial tumor, aneurysm, arteriovenous malformation or other space-occupying lesion.

_Stroke Code (Adams et al., 2007)._

The goal of the stroke code is to rapidly administer tPA in appropriately screened candidates. The onset of symptoms to treatment can be up to 180 minutes (or 270 minutes in selected patients), but the NIH recommendation of "door to drug" is within 60 minutes.
stroke code includes the following

- Rapid triage of patients as soon as they arrive in the ED.
- Immediate initiation of phlebotomy for appropriate blood tests, followed by CT scan or other equivalent imaging.
- First physician contact for history and exam occurring early in the ED visit. The NIH recommendation for timing of "door to first physician contact" for thrombolytic candidates is within 10 minutes.
- Rapid access to the best neurologic and radiologic expertise for evaluation of the patient and interpretation of the CT scan prior to treatment. The NIH recommendation for the timing of "door to initiation of CT scan" for thrombolytic candidates is within 25 minutes.

The following diagnostic evaluations should typically be performed (*Calvet et al.*, 2007).

- **Laboratory tests**
  - Complete blood count
  - Electrolytes (sodium, potassium, chloride, CO2), BUN, creatinine, glucose
  - Prothrombin time / international normalized ratio (INR)
  - Activated partial thromboplastin time (aPTT)
  - Cardiac biomarkers (troponin)
- **Electrocardiogram**
- **Brain and vascular imaging**
  - Magnetic resonance imaging MRI (preferred)/magnetic resonance angiography
  - Computed tomography/computed tomography angiography
  - CTA/carotid ultrasound, if symptoms referable to carotid distribution
Dosage and administration

Treatment should consist of tPA 0.9 mg/kg intravenously to a maximum dose of 90 mg. Ten percent of this dose should be given as a bolus over one to two minutes and the remainder infused over one hour (Adams et al., 2007).

Indications from three studies show that currently used doses of thrombolytic agents may be inadequate for lysis of large cerebral thrombi. The rate of thrombolysis correlates with the ratio of thrombus surface area to thrombus volume and with the local concentration of the thrombolytic agent. The accessible surface area of a thrombus occluding a large vessel such as the trunk of the middle cerebral artery is limited to the proximal and distal ends, and high concentrations of an agent administered intravenously may be difficult to achieve without doses so high as to pose excessive risk for posttreatment ICH (Metwally, 2010).

Treatment of hypertension (Adams et al., 2007)

Pretreatment

*Systolic >185 OR diastolic >110 mmHg
-Labetalol 10-20 mg IV over 1-2 min.
-May repeat OR nitropaste 1-2 inches; OR nicardipine infusion, 5 mg/hour, titrate up by 2.5 mg/hour at 5- to 15-minute intervals, maximum dose 15 mg/hour; when desired blood pressure attained, reduce to 3 mg/hour.

-If blood pressure does not decline and remains > 185/110 mmHg, do not administer rtPA.

During and after treatment

*Systolic 180 to 230 mmHg or Diastolic 105 to 120 mmHg
- Labetalol 10 mg IV over 1-2 minutes, may repeat every 10 to 20 minutes, maximum dose of 300 mg,

OR

- Labetalol 10 mg IV followed by an infusion at 2 to 8 mg/minute

*Systolic > 230 mmHg or Diastolic 121-140 mmHg

- Labetalol 10 mg IV over 1 to 2 minutes, may repeat every 10 to 20 minutes, maximum dose of 300 mg

OR

- Nicardipine infusion, 5 mg/hour, titrate up to desired effect by increasing 2.5 mg/hour every 5 minutes to a maximum of 15 mg/hour.

If blood pressure not controlled, consider sodium nitroprusside 0.5 mcg/kg/minute.

In general, following thrombolysis, repeated CT scanning is required to exclude secondary haemorrhage. Continuous heparin should be given 24 hours after thrombolysis with a target aPTT 1.5-2 times the initial values. Repeated angiography and ultrasound studies to exclude rethrombosis after 12-24 hours should be routinely performed (Metwally, 2010).

Complications of intravenous rt-PA

Thrombolytic therapy in acute ischemic stroke is based on the “re-canalization hypothesis,” reopening occluded vessels improves clinical outcome through regional reperfusion and salvage of threatened tissues. Several biologic factors may weaken the relationship of re-canalization to outcome in patients with acute ischemic stroke. In large occlusive disease, re-canalization may not be effective because of distal
embolization and microcirculatory occlusion. Re-canalization may exacerbate tissue injury by promoting reperfusion injury, excessive cerebral edema, and hemorrhagic transformation (*Rha and Saver, 2007*).

Reperfusion after ischemia causes oxidative stress, which is a result of overproduction of reactive oxygen species in mitochondria. This overproduction significantly limits the benefits of stroke therapies, and these ROS trigger many cellular and molecular events, including protein oxidation/nitrosylation/nitration, lipid peroxidation, and DNA damage, which can induce cell death following cerebral ischemia and reperfusion (*Sugawara and Chan, 2003*).

**Hemorrhagic complication of intravenous rt-PA**

The most feared complication in acute ischemic stroke is hemorrhagic transformation (HT) as it has devastating clinical consequences and is associated with an over ten-fold increase in mortality (*Berger et al., 2001*).

Although in clinical practice this complication may be less frequent than failure of treatment to recanalized occluded cerebral artery or early reocclusion, ICH seems to represent an important obstacle to the generalization of thrombolytic therapy (*Giuseppe et al., 2009*).

Intracerebral hemorrhage mostly occurs in the core of the infarcted area, thus suggesting that ischemic events can have an important role (*Savitz et al., 2007*).

In experimental models of focal cerebral ischemia, the basal lamina of the vessels and the extracellular matrix show an alteration and the adhesion between the microvessel cells and the extracellular matrix is dearranged so there can be an extravasation of blood elements. There is an increase in capillary permeability that comes along with an inrush of plasma components inside the brain tissue, an inflammatory reaction with
thrombin activation, and an increasing of many mediators such as platelet-activating factor, tumor necrosis factor α and bradykinin, which contribute to increase endothelial permeability. In addition, oxidative damage may increase hemorrhagic risk (Caplan, 2006).

Metalloproteinases

Matrix metalloproteinases (MMP) are involved in the hemorrhagic transformation, and their activation is partly responsible for the BBB disruption. MMPs represent a family of proteolytic enzymes combined with zinc, which acts normally on the remodeling of the extracellular matrix. Inappropriate activation can induce proteolysis of the matrix of the neurovascular unity (endothelium, astrocyte, and neuron). MMPs are liberated by the endothelium and the polynucleates at the inflammatory stage of ischemia and utilize type IV collagen and laminin as substrates. (Giuseppe et al., 2009). In some animal models of focal cerebral ischemia, activation of MMP-9 is associated with increased permeability of the BBB that leads to edema formation and hemorrhagic transformation (Sumii and Lo, 2002).

MMP-2 and MMP-9 released during the ischemic event can damage the vessel components, particularly type IV collagen, fibronectin, and laminin, thus altering the basal lamina of the cerebral vessels. In humans, elevation of MMP-9 is linked to the severity of ischemic stroke (Gautier et al., 2003), and the pretherapeutic MMP-9 rate is an independent predictor of the risk of hemorrhagic transformation related to thrombolysis (Montaner et al., 2003).

Risk factors for HT

Exact knowledge of mechanisms related to ICH after thrombolysis and the role of biomarkers could be useful in selecting patients that can
benefit from such treatment. Other elements must be taken in account for the genesis of rt-PA-related ICH: age, hypertension, diabetes mellitus or cerebral amyloid angiopathy, extent of early ischemic signs shown on brain CT scan or the volume of cerebral ischemic lesions on diffusion weighted MRI, and the presence of leukoaraiosis (Derex et al., 2005).

The first trials on rt-PA have provided evidence that higher doses of lytic agents lead to higher rates of sICH, so the dose was limited to 0.9 mg/kg up to 90 mg in total (Cocho et al., 2006).

Age has been consistently found to be a risk factor for sICH after thrombolysis for acute ischemic stroke (Derex et al., 2005). Recent data from several open-label studies on use of rt-PA have shown that the risk of sICH in the elderly is comparable to that of younger patients. Certain trial showed that the benefit–risk ratio of intravenous rt-PA can be favorable in carefully selected elderly stroke patients treated within three hours. The sICH rate was 4.4% in the group of patients aged 80 years or older included in this study (Berrouschot et al., 2005).

The Stroke Survey Group rt-PA analysis also concluded that it was not justified to systematically contraindicate thrombolysis for patients older than 80 years (Heuschmann et al., 2004).

Many authors have shown the importance of the baseline stroke severity in hemorrhagic risk after thrombolysis (Sylaja et al., 2006). The Multicentre tPA Acute Stroke Survey study showed that the NIHSS score was an independent marker of ICH, with an odds ratio of 1.38 for a one-point increase in the NIHSS score (Heuschmann et al., 2004).

Some authors on their report did not find a significant association of severity of neurological deficit at baseline with increased risk of sICH (Berrouschot et al., 2005). Moreover, the ECASS I trial showed that severity of neurological deficit at admission represented a risk factor for
hemorrhagic transformation and not for parenchymal hematoma (Derex et al., 2005).

Another factor which may contribute to the development of rt-PA-related sICH is hypertension during the first 24 hours after ischemic stroke (Ribo et al., 2004).

Experimental and human studies indicate that hyperglycemia predicts higher stroke mortality independently from stroke severity, stroke type, or age. These data suggest that hyperglycemia may directly contribute to poor outcomes by exacerbating acute brain injury (Capes et al., 2001). In the PROACT II study, there was an increased risk of sICH in patients with pretherapeutic glycemia higher than 200 mg/dl (Lindsberg et al., 2003).

The mechanism of hyperglycemia-related ICH is not clear. There are numerous animal experimental proofs that hyperglycemia provokes microvascular lesions as well as BBB damage, leading to hemorrhagic transformation of the cerebral infarction (Kase et al., 2001).

However some authors did not find that a history of diabetes mellitus was a risk factor for sICH, despite the fact that many patients with diabetes mellitus had elevated serum glucose at stroke onset (Berrouschot et al., 2005).

The significance of early ischemic changes on baseline brain CT scan as predictors of hemorrhagic transformation scan remains controversial (von Kummer, 2003).

With the advent of advanced MRI such as diffusion- (DWI) and perfusion-weighted imaging (PWI), it has been demonstrated in recent studies that in anterior circulation strokes, an acute DWI lesion volume >70 cm$^3$ has a high specificity for poor outcomes with or without therapy (Barak et al., 2008).
A retrospective multicenter study evaluated whether leukoaraiosis is a risk factor for sICH in patients treated with alteplase for anterior circulation stroke. All patients had received magnetic resonance imaging evaluation before thrombolysis and for statistical analysis. Leukoaraiosis in the deep white matter was dichotomized into absent or mild versus moderate or severe. The rate of sICH was significantly higher in patients with moderate to severe leukoaraiosis than in patients without relevant leukoaraiosis (Barber et al., 2000).

The risk of ICH after thrombolysis in ischemic stroke patients carrying old asymptomatic microbleeds (which can considered as a marker of microangiopathy, and of amyloid angiopathy) remains a controversial subject (Neumann-Haefelin et al., 2006). In a published pooled analysis of 570 patients, the presence of microbleeds was not predictive of sICH after thrombolysis except grade 3 microbleeds (Kakuda et al., 2005).

Some authors have suggested that the differences between symptomatic and asymptomatic ICHs are due to the intensity of bleeding rather than physiopathologic differences. For others, hemorrhagic infarctions and parenchymal hematomas after t-PA have a different clinical, etiologic, and biological significance (Fiehler et al., 2007). Benign hemorrhagic transformation can be associated with the natural history of ischemic stroke while parenchymal hematomas, especially the PH-type 2 (homogeneous hematomas with mass effect occupying 30% of ischemic lesion volume) could be linked to the t-PA itself and particularly to its impact on homeostasis (as demonstrated by elevation of fibrin degradation products after treatment) (Thomalla et al., 2007).

Any extension of the thrombolytic treatment window also implies an increased risk of HT. Data shows that the occurrence of HT in patients treated within three hours of symptom onset was 4.8%, while for those
treated between three and six hours after onset the occurrence rose to 6.4% (Hacke et al., 2008).

Although tPA can cause fatal or symptomatic brain hemorrhage, patients treated with tPA strictly following protocol have a higher likelihood of functional neurologic recovery. Thus, only physicians experienced in stroke management should use tPA to treat patients with acute stroke; inexperienced physicians are more likely to violate protocols, resulting in more brain hemorrhages and deaths (Metwally, 2010).

**Efficacy of intravenous thrombolysis**

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study group reported that patients with acute ischemic stroke who received alteplase within three hours after the onset of symptoms were at least 30% more likely to have minimal or no disability at three months than those who received placebo. One year after the publication of the NINDS study, the US Food and Drug Administration approved intravenous rt-PA as a treatment for acute ischemic stroke (Adams et al., 2003).

Negative thrombolytic studies differed from the NINDS trial in fundamental and important aspects, such as different thrombolytic drugs, different doses of rt-PA, and longer intervals between symptom onset and treatment. Among negative trials of intravenous rt-PA there was the first European Cooperative Acute Stroke Study (ECASS I), in which a higher dose of rt-PA was used (1.1 mg/kg) and patients were randomized up to six hours after the onset of symptoms (Hacke et al., 1995). In the ECASS II trial, the dose of rt-PA was identical to that used in the NINDS trial, but there was a six-hour treatment window, with most patients treated
after three hours. In this trial, the results were not in favor of treatment with alteplase (Hacke et al., 1998).

The Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS) study used a treatment protocol identical to that of the NINDS trial but randomized patients from three to five hours after stroke and also showed negative results (Clark et al., 1999).

Despite these findings, Hacke and colleagues in 2004 reported positive results of an intention-to-treat analysis of pooled data from randomized trials of rt-PA for ischemic stroke (NINDS, ECASS I, ECASS II, and ATLANTIS) that included 2775 patients treated up to six hours after symptom onset in more than 300 hospitals located in 18 countries. This analysis supported the results of the NINDS trial and demonstrated that treatment within three hours (and possibly up to 4.5 hours) of symptom onset is associated with a greater chance of a favorable outcome at three months.

On the basis of these different results the European Medicines Agency (EMEA) granted approval of alteplase in 2002 under condition that a study be initiated in order to assess the safety and efficacy of rt-PA in routine clinical practice; subsequently, the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST) was undertaken. SITS-MOST completed in 2007 and confirmed that alteplase is safe and effective when used in the first three hours after the onset of stroke in a wide range of clinical settings. The primary aim of the study was to establish whether the levels of safety seen in randomized controlled trial populations could be reproduced in routine clinical practice, and mainly concerned ICH. The results of this observational study showed that the proportion of patients who experience sICH was similar to that observed in randomized controlled trials. Moreover there
was a trend towards a reduced incidence of ICH in SITS-MOST when compared to NINDS study. A reduction in mortality within the first three months was also seen in SITS-MOST compared with randomized controlled trials (Wahlgren et al., 2007).

ECASS III is the second randomized trial (after the NINDS trial in 1995) to show significant treatment efficacy with intravenous alteplase in the unadjusted analysis of the primary end-point demonstrating that patients with acute ischemic stroke benefited from treatment when administered 3 to 4.5 hours after the onset of stroke symptoms (Hacke et al., 2008).

**Predictors of good outcome after thrombolysis:**

-Milder baseline stroke severity:

The initial severity of a stroke is a strong predictor of the functional and neurologic outcome and of the risk of death (Hacke et al., 2008). In the NINDS study, patients with a baseline NIHSS score of 20 were 11 times more prone to having sICH than patients with an NIHSS score of 5. The Multicentre tPA Acute Stroke Survey study also showed that the NIHSS score was an independent marker of ICH, with an odds ratio of 1.38 for a one-point increase in the NIHSS score. On the basis of these results, in some countries a NIHSS score of 25 represents a contraindication for alteplase administration (Micieli et al., 2009).

-Early treatment:

Early treatment remains essential. The effect size of thrombolysis is time-dependent. Some studies showed that treatment with alteplase is nearly twice as efficacious when administered within the first 1.5 hours after the onset of a stroke as it is when administered within 1.5 to 3 hours afterward (Hacke et al., 2008).
- Younger age:

Recent data from several open-label studies on use of rt-PA have shown that the risk of sICH in the elderly is comparable to that of younger patients. In certain Study, the rate of sICH increased with age from 4.9% in patients younger than 55 years to 10.3% in patients aged 75 years and older (Micieli et al., 2009).

-Normal pretreatment blood pressure:

A systolic blood pressure of 141–150 mm Hg was associated with the most favourable outcomes. Some studies showed that systolic blood pressure has a linear association with symptomatic haemorrhage and a U-shaped association with mortality and dependence at 3 months (Ahmed et al., 2009).

-Normal pretreatment blood glucose level

Baseline hyperglycemia is found more commonly in patients with preexisting diabetes but is also present in a significant proportion of nondiabetic patients. Multiple studies showed that in IV-tPA–treated stroke patients, admission hyperglycemia was independently associated with increased risk of death, SICH, and poor functional status at 90 days (Alexandre et al., 2009).

Normal CT scan

The ECASS I and ECASS II trials have shown that the presence of early ischemic change in more than one-third of the MCA territory before thrombolysis is accompanied by an increase in the hemorrhagic transformation risk and poor clinical outcome (Micieli et al., 2009).

Alteplase is still underused; it is estimated that fewer than 2% of patients receive this treatment in most countries, primarily because of delayed admission to a stroke center (Albers and Olivot, 2007). Other
factors have been reported to explain the underuse of this therapeutic approach to ischemic stroke as insufficient public warning and knowledge of stroke symptoms, the limited number of centers able to perform thrombolysis and an excessive fear of hemorrhagic complications (Reeves et al., 2005).

The future of t-PA for the treatment of patients with acute ischemic stroke largely depends on successfully attaining several goals including: (i) a better organization of the health care system, (ii) improvement of the thrombolytic properties of t-PA, (iii) inhibition of the deleterious effects of t-PA on the permeability of the neurovascular unit without interfering with its thrombolytic properties, (iv) attenuation of the neurotoxic effects of t-PA, and (v) extension of the time window. The organization of the health care system should include educational programs directed to the public and the development of acute stroke units staffed by personnel with expertise in the diagnosis and treatment of acute stroke (Giuseppe et al., 2009).

The improvement of the efficiency of t-PA as a thrombolytic agent may be based on the results of ongoing studies which are testing the effect of combined intravenous and intra-arterial thrombolysis in addition to the simultaneous use of t-PA and transcranial or local procedures (Giuseppe et al., 2009).

Moreover, because the effect of t-PA on the BBB permeability seems to be have an important role in the deleterious effects of t-PA itself in the ischemic brain, the combined therapy of t-PA and protectors of the integrity of the neurovascular unit might achieve promising results (Giuseppe et al., 2009).
Intra-arterial Thrombolysis

Intra-arterial therapy (IAT) is increasingly used in the treatment of acute stroke either as the primary modality for patients presenting 3 to 8 hours from symptom onset or as an adjuvant measure in patients treated with intravenous tissue plasminogen activator who do not improve in a timely fashion. Primary IAT has been shown to improve clinical outcome when administered 3 to 6 hours from symptom onset using intra-arterial thrombolytics (Ogawa et al., 2007), and is approved up to 8 hours using mechanical clot retrieval (Merci Retriever) or suction thrombectomy (Penumbra System) (Bose et al., 2008).

The primary goal of IAT is recanalization of the occluded artery and reperfusion of the ischemic territory. Recanalization has been shown to correlate with a better outcome in patients with stroke (Rha and Saver, 2007); however, this correlation may be confounded by several factors, including the time from symptom onset to recanalization and the degree of collateral circulation to the ischemic region (Higashida and Furlan, 2003) and the extent of infarct before recanalization (Albers et al., 2006). Therefore, it is not surprising that despite high rates of recanalization with IAT, the rate of functional independence is reported to be only 40% to 50% (Smith, 2006).

Intra-arterial therapy is currently applicable to a small subset of patients with ischemic stroke, but it will likely have an expanding role as new devices are introduced. These expanding applications of intra-arterial therapy for ischemic stroke lead to speculation regarding the availability of a sufficient number of operators to treat these patients (White et al., 2007).
IAT has several theoretic advantages over IV thrombolysis. For instance, with the coaxial microcatheter techniques, the occluded intracranial vessel is directly accessible and the fibrinolytic agent can be infused directly into the thrombus. This permits a smaller dose of fibrinolytic agent to reach a higher local concentration than that reached by systemic infusion and ideally allows more complete recanalization with lower total doses of thrombolytic. With the smaller dose, complications from systemic fibrinolytic effects, including intracranial hemorrhage, can theoretically be reduced. For these reasons, the treatment window for endovascular techniques can be extended beyond the typical IV window of 4.5 hours. This factor becomes particularly important in face of the relatively low number of patients who present within the time window for IV rtPA (Kleindorfer et al., 2008).

**Patient selection**

Intra-arterial therapy has been shown to be efficacious in opening occluded arteries in some patients with severe ischemic stroke. However, far from all patients with ischemic stroke are candidates for intra-arterial stroke therapy. Only patients with occlusion of relatively large intracranial arteries typically undergo recanalization intra-arterially (Smith et al., 2008).

Patients with NIHSS of less than 10 are quite unlikely to benefit from intra-arterial therapy, as they typically have normal results on cerebral angiograms or distal or recanalizing emboli (Fischer et al., 2005).

An initial evaluation with a noncontrast computerized tomography head scan is necessary. Patients with large territorial infarcts on CT scan are at a higher risk for hemorrhagic conversion following treatment and are therefore poor candidates for endovascular therapy (Vora et al., 2007).
The clinical application of CT perfusion scans has facilitated the pretreatment evaluation of “salvageable” tissue. A scan consistent with a mismatch between cerebral blood volume and cerebral blood flow or mean transient time (CBF or MTT, “penumbra” lesion volume) is a favorable patient selection criterion (Konstas et al., 2009).

Previous administration of intravenous tissue plasminogen activator is not a contraindication to IA intervention. However, the hemorrhagic complications in these patients are significantly higher, especially if urokinase was the arterial agent (Vora et al., 2007).

Limitations of IA Thrombolysis

The time to treatment for IA thrombolysis is longer compared to that of IV thrombolysis because there are logistical factors involved, such as the need to assemble the angiography team and confirm occlusion angiographically before administration of thrombolytics. One third of patients developed the stroke during cerebral angiography, which would make IA therapy quicker since most preliminary steps to IA thrombolysis had already occurred. One approach used to minimize the delay in thrombolysis using IA therapy is to use a combination of a reduced dose of IV rtPA (0.6 mg/kg) within 3 h and then continue therapy using IA thrombolysis in patients who do not respond to IV thrombolysis (IMS II, 2007).

Another disadvantage of IA thrombolysis is the invasiveness of angiography. However, the risk of serious complications is relatively low when the procedure is done by an experienced angiographer. In a large retrospective analysis of about 20,000 patients who underwent cerebral angiography at the Mayo clinic, stroke and death occurred in 0.15% and 0.06% of patients, respectively. TIA occurred in 2%. Other complications include access-site hematoma (4.2%); nausea, vomiting, or transient
hypotension (1.2%); anaphylaxis (0.03%); and acute renal failure (0.04%). Stroke occurred more frequently in patients with underlying atherosclerotic disease (0.25%) (Kaufmann et al., 2007).

The monetary cost of IA thrombolysis and associated hospitalization may be an issue; however, the cost savings resulting from decreasing stroke disability likely outweighs the initial expense of thrombolysis and acute hospitalization (Bershad and Suarez, 2008).
Intra-arterial Chemical Thrombolysis

Dosage and administration

Multiple protocols have been published to facilitate administration of IA thrombolysis; some of these employ IA thrombolysis with UK, scu-PA, or rtPA only, or a combination thrombolysis using a reduced dose IV rtPA within 3 h, followed by IA thrombolysis within 6 h of stroke onset (Bershad and Suarez, 2008).

The typical dose of IA rtPA is a maximum of 0.3 mg/kg or total dose of about 20-24 mg. The dose of IA urokinase ranges from 50,000-250,000 units given as a bolus over 5-20 min; this dose may be repeated up to a maximum cumulative dose of 1,000,000 to 2,000,000 units of UK. The dosing of reteplase is up to a maximum dose of 6-8 units given in aliquots of 0.1-1 units (Bershad and Suarez, 2008).

Anterior Circulation

The optimal window for IA thrombolysis in the anterior circulation has been investigated in multiple clinical trials. Overall, results show that IA treatment of acute MCA infarction outweights potential hemorrhagic risks when implemented within a 6-hour window from symptom onset. However, if the occlusion does not involve the horizontal MCA segment and the lenticuloostriate arteries, then the treatment window can be extended to 12 hours following symptoms (Tjoumakaris et al., 2009).

Middle Cerebral Artery

The PROACT-I and PROACT-II clinical trials were the first randomized trials to evaluate IA thrombolysis. PROACT II design included 180 patients with less than 6 hours of acute ischemic stroke symptoms who were suspected of having MCA occlusion. After a CT
scan excluded hemorrhage and showed no evidence of acute hypodensity or sulcal effacement in more than one third of the MCA territory, all patients underwent angiography to identify the site of thrombosis. If occlusion of M1 or M2 segment was found, the patient was randomized to either pro-urokinase or a control group. All patients received a periprocedural IV heparin drip for 4 hours and repeat angiogram at 1 and 2 hours to assess the status of thrombolysis. Mechanical disruption was not allowed in either group. The results showed that 40% of the treatment group versus 25% of the control group achieved the primary outcome of slight disability or better at 3 months. Recanalization was seen in 66% and 27% of the pro-UK and placebo groups, respectively. Mortality rates were similar in both groups: 25% and 27% for the IA pro-UK and placebo arms, respectively. Symptomatic intracerebral hemorrhage was more common in the IA pro-UK arm than in the placebo arm. Thus far, this is the only large randomized and controlled clinical trial demonstrating the efficacy of IA thrombolysis (Bershad and Suarez, 2008).

Recently, the MELT Japanese study group investigated the IA administration of UK in the setting of MCA stroke within 6 hours of onset. Although the study showed favorable 90-day functional outcome in the UK-treated patients with respect to controls, results did not reach statistical significance. Unfortunately, the investigation was aborted prematurely following the approval of intravenous r-TPA in Japan for the treatment of acute ischemic stroke (Ogawa et al., 2007).

Internal Carotid Artery

Occlusions of the proximal ICA generally have a better prognosis than intracranial occlusions. The presence of external-internal carotid collateral flow and the anastomosis at the circle of Willis account for this
observation. Patients with insufficient extracranial - intracranial anastomoses or an incomplete circle of Willis may be predisposed to developing significant neurologic symptoms. These patients are potential candidates for IA intervention. In these cases, mechanical thrombolysis, in addition to pharmacologic thrombolysis, is of paramount importance for recanalization (Tjoumakaris et al., 2009).

Among all possible occlusion sites within the anterior circulation, acute internal carotid artery terminus (TICA) occlusions carry the worst prognosis. Depending on the location and extent of the thrombus (T-shape or L-shape lesions), TICA lesions obstruct Willisiana collaterals, retrograde ophthalmic circulation, and lead to reduced leptomeningeal collateral capacity from the ipsilateral anterior cerebral artery if the anterior communicating artery is absent or the contralateral A1 is hypoplastic/atretic. Furthermore, if the thrombus is extensive enough to occlude the origin of a large posterior communicating artery, leptomeningeal collateral supply from the posterior cerebral artery may also be compromised (Lin et al., 2009).

Flint and colleagues in 2007 published a series of 80 patients with ICA occlusion who were treated with combinations of the Merci retriever with or without adjunctive endovascular therapy. Recanalization rates were higher in the combination group (63%) as opposed to the Merci group (53%). At a 3-month follow-up, 25% of patients had a good neurologic outcome, with their age being a positive predictive indicator. Overall, these results are encouraging, and IA intervention in select cases of acute ICA occlusion should be considered.
posterior circulation

Acute thromboembolic occlusion of the basilar artery (BA) is a relatively rare entity accounting for only 6%–10% of large-vessel strokes in humans (Smith,2007).

A stroke due to basilar artery occlusion has a very poor prognosis with mortality rate over 80% if patients are treated by standard medical therapy including anticoagulation (Schonewille et al.,2005).

It has been known that clinical factors increasing mortality following acute vertebra-basilar occlusion (VBO) include older age, coma at presentation, quadriparesis, time from stroke onset, presence of basilar atherosclerosis and absence of basilar artery collaterals (Smith,2007).

IA thrombolysis in acute VBO is the only life-saving therapy that has demonstrated the benefit with regard to mortality and outcome (Arnold et al.,2004).

The time window for thrombolysis in the posterior circulation has been thought to be longer than that of anterior circulation because of lower risk of hemorrhagic transformation (as a result of smaller infarct volumes), worse outcomes with conventional therapy, and additional pathophysiological differences (including collateral flow patterns) that may lead to a slower evolution of irreversible ischemia within this lesion (Ostrem et al.,2004).

Ecker et al. in 2002 found a significantly better clinical outcome in patients with acute VBO treated within 6 hours after symptom onset than in patients treated over 6 hours. However, Arnold et al. in 2004 found no significant association between time to treatment and clinical outcome in 40 patients treated with IA thrombolysis within 12 hours after symptom onset.

The IA thrombolysis significantly increases recanalization to 67% considering multiple case series. Recanalization is also significantly
associated with increasing survival and the clinical outcomes in survivors are favorable in 57% to 71% (Smith, 2007).

It is not uncommon to see early re-occlusion after thrombolysis of a VBO due to a high grade arteriosclerotic stenosis of the intracranial vertebral or basilar artery which can then be treated with angioplasty and/or stenting (Schulte et al., 2007).

Multimodal therapy has been described to be successful when intra-arterial therapy alone fails to achieve recanalization (Abou-Chebl et al., 2005). With aggressive intra-arterial thrombolysis with TPA as well as intravenous abciximab and the addition of angioplasty and stenting in the setting of >70% residual stenosis after thrombolysis, significantly greater complete recanalization has been reported with lower mortality and with no increase in symptomatic intracranial hemorrhage compared to intra-arterial TPA alone (Eckert et al., 2005).
Intra-arterial Mechanical Thrombolysis

Mechanical strategies have several advantages over pharmacologic thrombolysis and may be used as primary or adjunctive strategies. First, they lessen and may even preclude the use of chemical thrombolytics, in this manner very likely reducing the risk of ICH. Second, by avoiding the use of chemical thrombolytics, it is possible to extend the treatment window beyond the limit of 6–8 hours. Third, mechanically fragmenting a clot increases the surface area accessible to fibrinolytic agents and allows inflow of fresh plasminogen, which, in turn, may increase the speed of thrombolysis. Finally, clot-retrieval devices may provide faster recanalization and may be more efficient at coping with material resistant to enzymatic degradation, including excessive cross-linking in mature embolic clots and emboli composed of cholesterol, calcium, or other debris from atherosclerotic lesions (Nogueira et al., 2009).

As such, mechanical approaches with little or no thrombolytic agent have emerged as a key option for patients who have either a contraindication to pharmacologic thrombolysis, such as recent surgery or abnormal hemostasis or are late in their presentation (Nogueira and Smith, 2009).

The main potential disadvantage of mechanical revascularization is the possibility of occlusion or damage of perforating arteries, vessel dissection, or endothelial injury, which could lead to intracranial hemorrhage or endothelial flap stenosis and occlusion. Other problems include clot fragmentation because of microcatheter or device manipulation within the clot with distal embolic infarction and reduction in distal perfusion. However, embolic event may also occur during IV and/or IA thrombolysis (King et al., 2007).
The conceptual basis of the mechanical endovascular devices can be broadly categorized into the following categories: thrombectomy, thromboaspiration, thrombus disruption, augmented fibrinolysis, and thrombus entrapment (Nogueira et al., 2009).

**Endovascular thrombectomy**

Endovascular thrombectomy or thrombus retrieval has the advantage of providing rapid flow restoration with a potentially lower likelihood of clot fragmentation and distal embolism when compared with other endovascular techniques. The devices differ with regard to where they apply force on the thrombus, taking either a proximal approach with aspiration or “grasper” devices or a distal approach with basketlike or snarelike devices. A study comparing the effectiveness of these 2 approaches in a swine stroke model demonstrated that the proximal device allowed fast repeated application with a low risk of thromboembolic events and vasospasm but a significantly lower success rate in retrieving thrombus than the distal device. Some of the most widely used examples are the Merci retriever, the Neuronet device, the Phenox clot retriever, the Catch thrombectomy device and the Alligator retrieval device (Nogueira et al., 2009).

In a recent study that investigated the efficacy of current thrombectomy mechanisms, the Merci, Phenox, and Catch devices presented equal results with clot mobilization and retrieval, but the Phenox retriever had a superior performance in terms of preventing distal embolization because it was able to capture most of these clot fragments (Liebig et al., 2008).
**Endovascular thromboaspiration**

The functioning mechanism in this category uses an aspiration technique, which is suited for fresh non adhesive clots. These devices also have the advantage of less embolic material and decreased vasospasm. However, the often more complex design of these devices may make them more difficult to navigate into the intracranial circulation. Some examples in this category are the Penumbra system and the AngioJet system (*Nogueira et al.*, 2009).

The Penumbra system includes a reperfusion catheter that aspirates the clot and a ring-shaped retriever. The favorable results of a prospective multicenter trial conducted in the United States and Europe led to the approval of the device by the FDA for the endovascular treatment of acute ischemic stroke (*Bose et al.*, 2008).

The Penumbra System originally included 2 different revascularization options: 1) thrombus debulking and aspiration with a reperfusion catheter that aspirates the clot while a separator device fragments it and prevents obstruction of the catheter, and 2) direct thrombus extraction with a ring retriever while a balloon-guided catheter is used to temporarily arrest flow (*Nogueira et al.*, 2009).

The AngioJet system is a rheolytic thrombectomy device that uses high-pressure saline jets to create a distal suction, which gently agitates the clot face. The generated clot fragments are then sucked into the access catheter (*Nogueira et al.*, 2009).

**Thrombus Disruption**

There are several techniques available for mechanical clot disruption. The most common is probing the thrombus with a microguidewire. This technique appears to be useful in facilitating chemical thrombolysis. Alternatively, a snare can be used for multiple passes through the
occlusion to disrupt the thrombus. A snare can also be used for clot retrieval, mostly in situations in which the clot has a firm consistency or contains solid material (*Nogueira et al., 2009*).

Many studies have shown the feasibility and high efficacy of percutaneous transluminal angioplasty (PTA) in acute stroke. PTA may be particularly useful in cases of atherothrombotic disease in which the residual stenosis may reduce flow sufficiently to cause rethrombosis. Given the risks of procedural complications such as vessel rupture and distal embolization, this technique is generally reserved as salvage therapy for patients whose flow cannot be restored by more conservative methods. However, this technique has likely become safer with the use of low-pressure more complaint balloons (*Mangiafico et al., 2005*).

Two devices that use different laser technologies have been used to disrupt intracranial clots. The EPAR is a mechanical clot-fragmentation device based on laser technology. However, the emulsification of the thrombus is a mechanical thrombolysis and not a direct laser induced ablation. The photonic energy is converted to acoustic energy at the fiberoptic tip through creation of microcavitation bubbles (*Nogueira et al., 2009*).

The LaTIS laser device uses the slow injection of contrast material as a “light pipe” to carry the energy from the catheter to the embolus (*Nesbit et al., 2004*).

**Augmented fibrinolysis**

These devices, such as the MicroLysUS infusion catheter, use a sonographic micro-tip to facilitate thrombolysis through ultrasonic vibration. This is achieved by a combination of a noncavitating sonography, which reversibly separates fibrin strands, and acoustic streaming, which increases fluid permeation, resulting in increased drug-
thrombus surface interaction. The net result is enhanced clot dissolution without emboli. *(Nogueira et al., 2009).* Recent studies show a favorable outcome with the use of such devices for the endovascular management of acute ischemic stroke *(Mahon et al., 2003).*

The OmniWave Endovascular System is currently indicated to infuse thrombolytics and remove thrombus in the peripheral vasculature. This system is catheter-based and is delivered over a 0.018-inch guidewire. It works by directing low-power ultrasonic energy down a catheter wire that has been tuned to create cavitation bubbles that fracture the fibrin matrix of the thrombus without adversely damaging surrounding vessel walls. Thus, this device has a hybrid mechanism that uses augmented fibrinolysis as well as direct clot disruption to eliminate the occlusive thrombus without the use of thrombolysis *(Nogueira et al., 2009).*

**Thrombus Entrapment**

Stent placement of an acutely occluded intracranial vessel may provide fast recanalization by entrapping the thrombus between the stent and the vessel wall. This may be followed by thrombus dissolution via either endogenous or pharmacologic thrombolysis *(Nogueira et al., 2009).*

Self-expanding stents (SES) have several potential advantages over balloon-expandable stents in the context of acute stroke. SES are much more flexible and easier to navigate into the intracranial circulation. Indeed, higher rates of recanalization and lower rates of vasospasm and side-branch occlusion were noticed with SES than with balloon-mounted stents in a canine model of vessels acutely occluded with thromboemboli *(Levy et al., 2006).*

As opposed to acute coronary syndromes in which plaque rupture in an underlying atheroma is the most frequent culprit, most cases of acute intracranial vascular occlusions are related to an embolus in the absence
of any in situ vascular pathology. Therefore, balloon angioplasty with high-pressure balloons and balloon-expandable stents are typically not necessary to recanalize the vessel and may only increase the chance of serious complications such as vessel rupture or dissection. Finally, SES cause less endothelial damage and, therefore, may result in lower rates of early reocclusion or late stent stenosis \textit{(Nogueira et al., 2009)}.

A total of 5 intracranial SES are currently available: 1) the Neuroform stent, 2) the Enterprise stent, 3) the LEO stent, 4) the Solitaire/Solo stent, and 5) the Wingspan stent. The first 4 devices are currently marketed for stent-assisted coil embolization of wide-neck aneurysms, whereas the Wingspan stent is approved for the treatment of intracranial atherosclerosis disease. \textit{(Nogueira et al., 2009)}.

SES with higher radial force (eg, Wingspan) will likely play a key role in patients with acute stroke related to intracranial atherosclerotic disease \textit{(Henkes et al., 2005)}.

Their use in acute ischemic events has been investigated in several trials. In two studies investigating the Neuroform and Wingspan stents, recanalization rates ranged from 67% to 89% and early follow-up showed small or no restenosis rates \textit{(Zaidat et al., 2008)}.

Stent placement of the proximal cervical vessels may also be required to gain access to the intracranial thrombus with other mechanical devices or catheters. Furthermore, brisk antegrade flow is essential for the maintenance of distal vascular patency, as particularly evident in patients with severe proximal stenoses who commonly develop rethrombosis after vessel recanalization \textit{(Nogueira et al., 2009)}. In a recent series, 23 of 25 patients with acute or subacute cervical ICA occlusions were successfully revascularized with this technique \textit{(Jovin et al., 2005)}.
Temporary Endovascular Bypass.

As discussed above, stents may result in high recanalization rates over a relatively short procedural time. The need for an aggressive antithrombotic regimen after stent implantation remains one of the major limitations to its use in acute stroke. However, the advent of closed-cell stents has allowed resheathing/removal of the stent after recanalization is achieved, moderating the need for dual antiplatelet therapy, which could potentially increase the risk of hemorrhagic conversion of the infarct. In addition, this technique should eliminate the risk of delayed in-stent stenosis (Nogueira et al., 2009).

Kelly et al in 2008 reported a case in which partial deployment of an Enterprise stent resulted in immediate recanalization of an occluded MCA that was refractory to IV and IA rtPA, IA abciximab, and mechanical manipulation. The unconstrained portion of the stent expanded and acted as a temporary bypass to circumferentially displace and structurally disrupt the occlusive clot while additional abciximab was administered through the guiding catheter. The partially expanded stent was then reconstrained and removed 20 minutes later.

A similar approach can be theoretically applied to other reconstraining stents such as the Leo or the Solitaire/Solo. This temporary endovascular bypass technique is the main mechanism for the use of the ReVasc device, an SES-like device recently acquired by Micrus Endovascular (Nogueira et al., 2009).

Mechanical approaches in global reperfusion or flow augmentation

Global reperfusion or flow augmentation focuses on increasing cerebral blood flow to perfuse the tissue bed distal to the occlusive thrombus via leptomeningeal and/or circle of Willis collaterals. The
antegrade component of flow augmentation plays a direct role only in occlusions proximal to the circle of Willis, whereas most of the tissue reperfusion seen in cases of distal branch occlusions relies on increased flow to leptomeningeal collaterals with resultant retrograde filling of the occluded vessel down to the level of the occlusive thrombus. (Nogueira et al., 2009).

These flow augmentation strategies may potentially lead to better recanalization rates when used as an adjunct to antegrade reperfusion treatments. In addition, improvement in CBF should result in greater delivery of thrombolytic drugs to the occlusion site, theoretically leading to higher recanalization rates with systemic thrombolysis. Given the lesser degree of complexity involved in collateral perfusion augmentation, these techniques could potentially result in shorter reperfusion times compared with many recanalization therapies (Nogueira et al., 2009).

Flow augmentation can be achieved by either pharmacologic (eg, IV phenylephrine infusion) (Mistri et al., 2006) or mechanical approaches (eg, the NeuroFlo device). The NeuroFlo device is a dual balloon catheter uniquely designed for partial occlusion of the aorta above and below the origin of the renal arteries (Lylyk et al., 2005).

This device appears to work through mechanical flow diversion from the high-resistance lower body to the lower resistance cerebral circulation. Experimental evidence suggests that NeuroFlo increases global cerebral perfusion within minutes of balloon inflation, with little or no increase in mean arterial blood pressure. A new generation of the NeuroFlo catheter that allows distal access to intracranial vasculature is currently being developed. This will provide the ability to perform IA recanalization therapies while promoting flow augmentation through partial aortic obstruction (Nogueira et al., 2009).
Mechanical approaches in transvenous retrograde reperfusion or flow reversal

This experimental treatment technique, transvenous retrograde reperfusion or flow reversal, focuses on reversing the cerebral flow direction from arteries-capillaries-veins to veins-capillaries-arteries. Partial or venous flow reversal.

The first attempt of flow reversal was the retrograde transvenous neuroperfusion (RTN), which used an external pump to harvest arterial blood from the subject’s femoral artery and to transport the blood through 2 catheters placed into each of the transverse sinuses near the torcula. The blood was directed retrograde, opposite to normal venous flow, through the central, deep, and superficial sinuses and veins to reach the capillary bed. An abstract reported the safety and feasibility of RTN treatment in 6 patients; however, larger clinical trials have not been reported (Nogueira et al., 2009).

Complete arteriovenous flow reversal.

The ReviveFlow system is a novel method of cerebral flow reversal in which a balloon guide catheter is placed in the cervical ICAs and jugular veins on 1 or both sides of the neck. The balloons are subsequently inflated, and blood is aspirated via an external pump system from the proximal ICA and infused in the distal internal jugular vein. The end result is total reversal of the cerebral circulation and perfusion of the venous system with arterial blood into the capillary bed, which is now physiologically proximal to the occluded artery. This device is currently undergoing preclinical studies (Nogueira et al., 2009).
Neuroprotection In Stroke

Neuroprotection is any strategy, or combination of strategies, that antagonizes, interrupts, or slows the sequence of injurious biochemical and molecular events that, if left unchecked, would eventuate in irreversible ischemic injury (Ginsberg et al., 2008).

The concept of neuroprotection mainly came from the studies of the pathology and pathophysiology of ischemic brain injury. It has been well documented that abrupt deprivation of oxygen and glucose to neuronal tissues elicits a series of pathological cascades, leading to spread of neuronal death. Of the numerous pathways identified, excessive activation of glutamate receptors, accumulation of intracellular calcium cations, abnormal recruitment of inflammatory cells, excessive production of free radicals, and initiation of pathological apoptosis are believed to play critical roles in ischemic damage, especially in the penumbral zone. Thus, it is logical to suggest that if one is able to interrupt the propagation of these cascades, at least part of the brain tissue can be protected. The phenomenon of the "ischemic cascade" has been described, and each step along this cascade provides a target for therapeutic intervention (Tuttolomondo et al., 2009).

One action of neuroprotective agents limits acute injury to neurons in the penumbra region or rim of the infarct after ischemia. Neurons in the penumbra are less likely to suffer irreversible injury at early time points than are neurons in the infarct core. Many of these agents modulate neuronal receptors to reduce release of excitatory neurotransmitters, which contribute to early neuronal injury. Other neuroprotective agents prevent potentially events associated with return of blood flow. Returning blood contains leukocytes that may occlude small vessels and release toxic products (Tuttolomondo et al., 2009).
Several new strategies are currently emerging, based on recent advances in our understanding of molecular pathways that could be considered as potential therapeutic targets \textit{(Tuttolomondo et al., 2009)}.

\textbf{N-methyl-D-aspartate receptors as a target for neuroprotection}

NMDA receptor subunits (e.g., NR1, NR2A-D) are expressed in distinct spatial and temporal patterns throughout development, suggesting that the receptor subunits may enable unique functions. These receptors are critical for neural plasticity, normal development of the nervous system, and survival of the organism \textit{(Tuttolomondo et al., 2009)}.

Kynurenic acid is a selective antagonist at the glycine coagonist site of the NMDA receptor complex at low concentration, and it is a broad-spectrum excitatory amino acid receptor blocker at high concentration. Kynurenic acid provides neuroprotection in animal models of cerebral ischemia only at very high doses as it hardly crosses the blood-brain barrier. The neuroprotective effect of L-kynurenine sulfate, a precursor of kynurenic acid, was therefore studied because L-kynurenine readily crosses the blood-brain barrier. The studies on mice and gerbils showed that the administration of L-kynurenine can elevate the brain concentration of kynurenic acid to neuroprotective levels, suggesting the potential clinical usefulness of L-kynurenine for the prevention of neuronal loss \textit{(Gigler et al., 2007)}.

Cyclooxygenase-2 (COX-2) enzyme increases abnormally during excitotoxicity and cerebral ischemia and promotes neurotoxicity. Some authors have shown that the EP1 receptor is important in mediating PGE2 toxicity. They tested the hypothesis that pretreatment with a highly selective EP1 receptor antagonist, ONO-8713, would improve stroke outcome and that post treatment would attenuate NMDA-induced acute excitotoxicity and protect organotypic brain slices from oxygen glucose
deprivation (OGD)-induced toxicity. They found that the EP1 receptor propagates neurotoxicity and that selective blockade could be considered as a potential preventive and/or therapeutic tool against ischemic/hypoxic neurological conditions (Ahmad et al., 2008).

**Reactive oxygen species (ROS) as a target for neuroprotection**

Free radicals are important in causing neural cell injury during cerebral infarction. The overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is a common underlying mechanism of many neuropathologies, as they have been shown to damage various cellular components, including proteins, lipids and DNA (Slemmer et al., 2008). Therefore, treatment with antioxidants may theoretically act to prevent propagation of tissue damage and improve both the survival and neurological outcome. Several such agents of widely varying chemical structures have been investigated as therapeutic agents for acute CNS injury (Valko et al., 2007).

Disodium 2,4-disulphophenyl-N-tert-butylnitrone (NXY-059) nitrone free radical trapping compound, has been shown to be neuroprotective in models of ischemic stroke (Tuttolomondo et al., 2009).

Marshall et al. in 2003 examined the efficacy of this drug when administered 4 hours after onset. They found that NXY-059 is an effective neuroprotective agent when administered 4 hours after pMCAO in a primate species, attenuating both motor and spatial neglect. The compound also substantially lessened the volume of cerebral damage.

In human subject setting, Stroke-Acute Ischemic NXY Treatment (SAINT) I and II trials were randomized, placebo-controlled, double-blind trials to investigate the efficacy of NXY-059 in patients with acute ischemic stroke. Authors conclude that NXY-059 is ineffective for
treatment of AIS within 6 hours of symptom onset and also ineffective in the prevention of alteplase-associated hemorrhage (Diener et al., 2008).

Hydroxyl radicals as a target for neuroprotection

Edaravone is a scavenger of hydroxyl radicals, had significant functional improvement. Shinohara et al. in 2009 conducted a multicenter randomized trial of edaravone intravenously and a control drug, sodium ozagrel, a thromboxane A(2) synthase inhibitor, intravenously in acute noncardioembolic ischemic stroke. The authors concluded that edaravone was at least as effective as ozagrel for the treatment of acute noncardioembolic ischemic stroke.

Ueno et al. in 2009 tested the hypothesis that edaravone has protective effects against white matter lesions (WML) and endothelial injury. The authors showed that edaravone enhanced spatial memory improvement but not motor function, and axonal damage were significantly improved with treatment of edaravone. They also indicated that treatment with edaravone provides protection against WML through endothelial protection and free radical scavenging and suggested that edaravone is potentially useful for the treatment of cognitive impairment.

Another study investigated the effect of edaravone on the outcome of patients with acute lacunar infarction. It showed that Edaravone improves the outcomes of patients with acute lacunar infarction especially motor palsy (Ohta et al., 2009).

Citicoline (cytidine-5'-diphosphocholine or CDP-choline) is a precursor essential for the synthesis of phosphatidylcholine, one of the cell membrane components that is degraded during cerebral ischemia to free fatty acids and free radicals. Animal studies suggest that citicoline may protect cell membranes by accelerating resynthesis of phospholipids
and suppressing the release of free fatty acids, stabilizing cell membranes, and reducing free radical generation. Numerous experimental stroke studies with citicoline have shown improved outcome and reduced infarct size in both ischemic and hemorrhagic stroke models. A meta-analysis of four randomized US clinical citicoline trials concluded that treatment with oral citicoline within the first 24 h after a moderate to severe stroke is safe and increases the probability of complete recovery at 3 months (Tuttolomondo et al., 2009).

*Alpha-Amino -3-hydroxy -5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors as a target for neuroprotection*

Glutamate is the major excitatory amino acid transmitter within the CNS. Glutamate receptors are found localized at the synapse within electron dense structures known as the postsynaptic density (PSD). Localization at the PSD is mediated by binding of glutamate receptors to submembrane proteins such as actin and PDZ containing proteins. PDZ domains are conserved motifs that mediate protein-protein interactions and self-association. In addition to glutamate receptors PDZ containing proteins bind a multitude of intracellular signal molecules including nitric oxide synthase. In this way PDZ proteins provide a mechanism for clustering glutamate receptors at the synapse together with their corresponding signal transduction proteins (Tuttolomondo et al., 2009).

Lin et al. in 2008 used the oxygen and glucose deprivation (OGD) paradigm in cultured cortical neurons as an in vitro approach to elucidate the mechanism of protection conferred by glutamate preconditioning. They showed that neurons preconditioned with glutamate exhibited resistant to damage induced by OGD and the ischemic tolerance
depended on the duration of preconditioning exposure and the interval between preconditioning exposure and test challenge.

**Activated protein c a target for neuroprotection**

Physiological proteolytic activation of protein C by thrombin occurs on the surface of the endothelial cell and involves the 2 membrane receptors, thrombomodulin and endothelial protein C receptor (EPCR) (*Dahlba and Villoutreix, 2005*). Binding of thrombin to thrombomodulin on the endothelial surface shields thrombin’s procoagulant exosite I and promotes its anticoagulant properties by activation of protein C by the thrombin-thrombomodulin complex. This reaction is augmented by localization of protein C on the endothelial surface by its binding to EPCR. The anticoagulant actions of APC are primarily based on the irreversible proteolytic inactivation of factors Va and VIIIa with contributions by various cofactors. These anticoagulant APC cofactors comprise both proteins and lipids, including protein S, factor V, high-density lipoprotein, anionic phospholipids (eg, phosphatidylserine, cardiolipin), and glycosphingolipids (eg, glucosylceramide) (*Tuttolomondo et al., 2009*).

Shibata et al. in 2001 examined the effects of APC in a murine model of focal ischemia. The authors showed that APC given before or after onset of ischemia restored cerebral blood flow, reduced brain infarct volume and brain edema, eliminated brain infiltration with neutrophils, and reduced the number of fibrin-positive cerebral vessels. So APC appear to be neuroprotective in stroke models although bleeding complications may limit the pharmacologic utility of APC.

Guo et al. in 2009 compared the 3K3A-APC mutant with 80% reduced anticoagulant activity and wild-type (wt)-APC. The authors showed that human 3K3A-APC protected human brain endothelial cells (BECs) from
oxygen/glucose deprivation with 1.7-fold greater efficacy than wt-APC. 3K3AAPC compared with wt-APC multi-dosing therapy after dMCAO significantly improved functional recovery and reduced the infarction volume. The wt-APC, but not 3K3A-APC, significantly increased the risk of intracerebral bleeding as indicated by a 50% increase in hemoglobin levels in the ischemic hemisphere. Thus, 3K3AAPC offers a new approach for safer and more efficacious treatments of neurodegenerative disorders and stroke with APC.

Wang et al. in 2009 used neuronal and brain endothelial cell injury models and middle cerebral artery occlusion in mice to compare efficacy and safety of drotrecogin-alfa activated, a hyperanticoagulant form of APC and human 3K3A-APC, an APC nonanticoagulant mutant. The authors concluded that nonanticoagulant 3K3A-APC exhibits greater neuroprotective efficacy with no risk for bleeding compared with drotrecogin-alfa activated.

**Neuronal Ca(2+) and Na(+) channels as a target for neuroprotection**

Excessive calcium entry into depolarized neurons contributes significantly to cerebral tissue damage after ischemia. Included in the sequence of events leading to neuronal death in ischemic tissue following stroke is an excessive and toxic rise in the intracellular Ca(2+)-concentration, predominantly due to an influx of Ca2+ through nonselective cation channels as well as Ca(2+)-channels. Neuronal voltage-gated cation channels regulate the transmembrane flux of calcium, sodium and potassium. Neuronal ischaemia occurring during acute ischaemic stroke results in the breakdown in the normal function of these ion channels, contributing to a series of pathological events leading to cell death. A dramatic increase in the intracellular concentration of
calcium during neuronal ischaemia plays a particularly important role in the neurotoxic cascade resulting in stroke-related acute neurodegeneration. One approach to provide therapeutic benefit following ischaemic stroke has been to target neuronal voltage-gated cation channels, and particularly blockers of calcium and sodium channels, for post-stroke neuroprotection *(Tuttolomondo et al., 2009)*.

With regard of possible neuroprotective properties of calcium channel blockers in acute stroke treatment Shah et al. in 2007 performed a retrospective study to determine the angiographic and clinical outcomes among patients treated with Intrarterial nicardipine administered as 2.5-5 mg dose either alone or adjunct to intra-arterial thrombolysis. Authors concluded that Intra-arterial delivery of nicardipine in doses up to 5 mg is well tolerated among patients with acute ischemic stroke but further studies are required to determine the potential efficacy of this approach with or without thrombolytics.

*Caspases as a target for neuroprotection*

Number of studies have validated the importance of caspase activation in ischemia-induced brain damage. Caspases participate in both the initiation and execution phases of apoptosis, and play a central role in neuronal death after global cerebral ischemia. In focal ischemia, apoptosis occurs in the penumbra during the secondary phase of expansion of the lesion. However, ultrastructural and biochemical analysis have also shown signs of apoptosis in the initial lesion, or infarct core, which is traditionally considered necrotic. Specific caspase pathways are activated in the core and in the penumbra, and participate in both cytoplasmic and nuclear apoptotic events, not withstanding their initial classification as activator or initiator caspases. This confirms that caspase inhibition holds tremendous neuroprotective potential in stroke
and other apoptosis-related degenerative diseases (Onténiente et al., 2003).

Active caspase-3 was expressed in the ischemic cortex from 5 to 48 h after stroke, whereas beta-catenin markedly degraded at 24 and 48 h after stroke. The caspase 3-specific inhibitor, Z-DQMD-FMK, attenuated beta-catenin degradation, but it did not affect phosphorylation of both beta-catenin and glycogen synthase kinase-3beta. In conclusion, beta-catenin degraded after stroke, and its degradation was caspase-3 dependent (Zhang et al., 2008).

Changes in caspase-3, Abeta and beta-site APP cleaving enzyme (BACE1) levels were detected in rat striatum on different days after middle cerebral artery occlusion using immunostaining. Xiong et al. in 2008 found that the positive labeled cells of activated caspase-3, Abeta, and BACE1 were significantly and time dependently increased in the ipsilateral striatum. Thus, these authors demonstrated that caspase-3 inhibition attenuated ischemia-induced Abeta formation by reducing BACE1 production and activity. On this basis caspases may represent a possible therapeutic target of neuroprotection in acute ischemic stroke setting.

Pharmacological inhibition of caspases may improve stroke outcome not only by reducing apoptotic brain damage but also by attenuating stroke-induced immunodeficiency. Braun et al. in 2007 investigated the effects of systemic administration of the novel, non-toxic caspase-inhibitor quinolyl-valyl-O-methylaspartyl-[2,6-difluorophenoxy]-methyl ketone (Q-VD-OPH) on stroke-induced neuronal and lymphocyte apoptosis, susceptibility to infections, and mortality in a murine model of stroke induced by middle cerebral artery occlusion. Q-VD-OPH reduced ischemic brain damage and stroke-induced programmed cell death in
thymus and spleen, decreased susceptibility to post stroke bacteremia, and improved survival.

**GABA receptors as a target for neuroprotection**

Zhou et al. in 2008 conducted a study to investigate whether the enhancement of GABA receptor activity could inhibit NMDA receptor-mediated nitric oxide (NO) production by neuronal NO synthase (nNOS) in brain ischemic injury. The results showed that both the GABA(A) receptor agonist muscimol and the GABA(B) receptor agonist baclofen had neuroprotective effect, and the combination of two agonists could significantly protect neurons against death induced by ischemia/reperfusion. These results suggest that GABA receptor agonists may serve as a potential and important neuroprotectant in therapy for ischemic stroke.

Another study demonstrated that Co-activation of GABA A and GABA B receptors results in neuroprotection during in vitro ischemia. However, it is unclear whether this mode of action is responsible for its neuroprotective effects in animal models of ischemia in vivo, and the precise mechanisms are also unknown. This study compared the neuroprotective efficacies of muscimol, a GABA A receptor agonist, and a GABA B receptor agonist baclofen in rat brain ischemia. The additive neuroprotection could be obtained in the hippocampal CA1 pyramidal cells prominently when muscimol and baclofen were co-applied (Xu et al., 2008).

**Minocycline as a neuroprotective**

The tetracycline derivative, minocycline, has been found recently to have multiple immunomodulatory properties that are not related to their antimicrobial activity. These studies have generated strong interests in the
mechanisms of minocycline, as its administration can attenuate the severity of a spectrum of neurological diseases, including in animal models of MS, ischemia, amyotrophic lateral sclerosis, Parkinson’s disease, and Huntington’s disease (Suk, 2004).

Minocycline has recently been reported to have neuroprotective effects in models of global and focal ischemia. The minocycline-induced reduction in infarct size and increased survival of hippocampal neurons after focal or global ischemia with reduction of IL-1β-converting enzyme, COX-2, and NOS mRNA in affected brain regions (Giuliani et al., 2005).

In vitro, minocycline prevents the excitotoxicity of glutamate on neurons, presumably via the inhibition of N-methyl-D-aspartate-induced activation of microglia (Tikka and Koistinaho, 2001).

Hypothermia

The neuroprotective effect of induced hypothermia (pre-, intra-, and post-ischemia) has been well described in animal models of focal and global ischemia, with even slight reductions of the body temperature (mild to moderate hypothermia, 33–35°C) effective in reducing ischemic brain damage (van der Worp et al., 2007).

For acute ischemic stroke systemic hypothermia has been shown to be feasible with surface cooling and intravascular systems, and clinical trials on safety and efficacy of hypothermia are ongoing (Lyden et al., 2005).

Hypothermia may reduce damage from excitotoxins, inflammation, free radicals, and necrosis. This could lead to longer neuronal survival and improved outcome after restoration of blood flow through revascularization methods such as thrombolysis. It may also reduce
edema after ischemia and lower the risk of postischemic hemorrhage (Lyden et al., 2006).

Terms used to describe hypothermia are not clearly defined. Most consider severe hypothermia as temperature below 28°C, moderate as 28°C to 34°C, and mild as 34°C to 36°C (Lyden et al., 2006).

Systemic hypothermia, induced by an ice blanket, ice cap or alcohol sponge bath has long been used clinically for fever patients, requiring little and simple equipment. But this can induce shivering and discomfort for patients and make it harder to control the temperature, or even the need for general anesthesia to weaken this uncomfortable feeling. For local cooling of the head, some studies applied the method of perfusing cold blood through the carotid artery, cold liquid through cerebral ventricles or topical hypothermia on the surface of head (Horn et al., 2006).

In experimental studies, some investigators used jugular infusion of cold saline to treat infarcted rats (Hsiao et al., 2007). Some investigators even implanted a small metal coil between the temporalis muscle and adjacent skull to induce the local brain hypothermia (Clark and Colbourne, 2007).

Hypothermia induced with cold saline has been shown to have neuroprotective effects against brain ischemia, but the optimal temperature of the saline has not been determined yet (Wu et al., 2009). Ding et al. perfused 6 ml of 20°C saline into the infarction region supplied by MCA in rats through a micro-catheter, which led to a protective effect in the brain (Ding et al., 2004).
Management Of Hypertension In Stroke Patients

An acute hypertensive response occurs within 24 h in up to 80% of patients with acute stroke (Willmot et al., 2004). This response is an increase of blood pressure above normal (140 mm Hg systolic or 90 mm Hg diastolic) or above pre-existing levels in previously hypertensive patients (Tikhonoff et al., 2009).

The primary cause of the hypertensive response is damage or compression of specific regions in the brain that regulate the activity of the autonomic nervous system (Qureshi, 2008).

Pre-existing hypertension, diabetes mellitus, high concentrations of serum creatinine, and the Cushing reflex (a reactive increase in blood pressure in response to raised intracranial pressure) can all exacerbate the rise in blood pressure. Headache, urine retention, infection, and stress associated with admission to hospital can lead to an imbalance in the autonomic nervous system, activate the sympathetic adrenomedullary pathway, and raise the concentrations of circulating catecholamines and inflammatory cytokines, all of which can contribute to the hypertensive response (Tikhonoff et al., 2009).

Blood pressure tends to decline spontaneously without pharmacological intervention in the first few days to weeks after stroke onset. The change in blood pressure after acute stroke is also associated with the severity of the neurological deficits caused by the stroke (Christensen et al., 2002). A low to normal blood pressure after acute stroke usually indicates extensive brain damage or concurrent coronary artery heart disease (Bath et al., 2003).

Systolic blood pressure has a linear association with symptomatic haemorrhage and a U-shaped association with mortality and dependence
at 3 months: a systolic blood pressure of 141–150 mm Hg was associated with the most favourable outcomes (Ahmed et al., 2009).

In patients with acute stroke, blood pressure should be reduced gradually with special attention for possible contraindications. The decrease in blood pressure should not exceed 10–20% of the initial level because of the higher set point of the autoregulation of cerebral blood flow in hypertensive patients and to avoid the risk of poor perfusion of affected brain area (Adams et al., 2007).

In case of occlusive or severely stenotic atherosclerotic disease of the main arteries that sustain blood flow to the brain, decreasing blood pressure can cause cerebral ischaemia, particularly when the collateral circulation is impaired (Rothwell et al., 2003).

Indications to actively lower blood pressure are coexisting critical conditions, such as hypertensive encephalopathy, aortic dissection, heart failure, acute myocardial infarction, acute renal failure, or preeclampsia and eclampsia (Tikhonoff et al., 2009).

**Treatment of hypertension in patient not eligible for thrombolysis (Adams et al., 2007)**

Systolic < 220 OR diastolic < 120

- Observe unless other end-organ involvement, e.g., aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy.

- Treat other symptoms of stroke such as headache, pain, agitation, nausea and vomiting.

- Treat other acute complications of stroke, including hypoxia, increased intracranial pressure, seizures or hypoglycemia.
Systolic > 220 OR diastolic > 120

-Labetalol 10-20 mg IV over 1-2 min.

-May repeat or double every 10 min. (maximum dose 300 mg) or nicardipine 5 mg/hr IV infusion as initial dose; titrate to desired effect by increasing 2.5 mg/hr every 5 min. to maximum of 15 mg/hr.

- Aim for a 15% reduction of blood pressure.

Diastolic > 140

- Nitroprusside 0.5 microgm/kg/min. IV infusion as initial dose with continuous blood pressure monitoring. Aim for a 10% to 15% reduction of blood pressure.

Management of previously treated hypertensive patients with acute stroke

Whether ongoing therapy to lower blood pressure should be continued or stopped in patients with acute stroke still needs to be resolved by proper evidence from randomized clinical trials. The SITS-ISTR investigators recently published a retrospective non-randomised analysis, which indicated that withholding antihypertensive therapy for up to 7 days after an ischaemic event in patients with a history of hypertension was associated with a worse outcome, whereas initiation of antihypertensive therapy in newly recognised moderate hypertension was associated with a favourable outcome (Ahmed et al., 2009).
Management Of Ischemic Cerebral Edema

General Measures for Managing Cerebral Edema

Optimizing Head and Neck Positions

Finding the optimal neutral head position in patients with cerebral edema is essential for avoiding jugular compression and impedance of venous outflow from the cranium, and for decreasing CSF hydrostatic pressure. In normal uninjured patients, as well as in patients with brain injury, head elevation decreases ICP. These observations have led most clinicians to incorporate a 30° elevation of the head in patients with poor intracranial compliance (Ng et al., 2004). Head position elevation may be a significant concern in patients with ischemic stroke, however, it may compromise perfusion to ischemic tissue at risk (Ropper et al., 2004).

Ventilation and Oxygenation

Hypoxia and hypocapnia are potent cerebral vasodilators and should be avoided in patients with cerebral edema (Rabinstein, 2006). It is recommended that any patients with GCS scores less than or equal to 8 and those with poor upper airway reflexes to be intubated for airway protection (Eccher and Suarez, 2004).

Management of Fever

Numerous experimental and clinical studies have demonstrated the deleterious effects of fever on outcome following brain injury, which theoretically result from increases in oxygen demand, although its specific effects on cerebral edema have not been elucidated. Therefore, normothermia is strongly recommended in patients with cerebral edema, irrespective of underlying origin. Acetaminophen is the most common agent used, and is recommended to avoid elevations in body temperature.
Other surface cooling devices have demonstrated some efficacy (Eccher and Suarez, 2004).

Management of hyperglycemia

Evidence from clinical studies in patients with ischemic stroke suggests a strong correlation between hyperglycemia and worse clinical outcomes. Hyperglycemia can also exacerbate brain injury and cerebral edema (Bruno et al., 2004). Also, significantly improved outcome has been reported in general ICU patients with good glycemic control (van den Berghe et al., 2001).

Nutritional Support

Prompt institution and maintenance of nutritional support is imperative in all patients with acute brain injury. Unless contraindicated, the enteral route of nutrition is preferred. Special attention should be given to the osmotic content of formulations, to avoid free water intake that may result in a hypoosmolar state and worsen cerebral edema (Ropper et al., 2004).

Specific Measures for Managing Cerebral Edema

Controlled Hyperventilation

Based on principles of altered cerebral pathophysiology associated with brain injury, controlled hyperventilation remains the most efficacious therapeutic intervention for cerebral edema, particularly when the edema is associated with elevations in ICP. A decrease in PaCO2 by 10 mmHg produces proportional decreases in rCBF (and decreases in CBV in the intracranial vault), resulting in rapid and prompt ICP reduction (Eccher and Suarez, 2004).
Overaggressive hyperventilation may actually result in cerebral ischemia. Therefore, the common clinical practice is to lower and maintain PaCO2 by 10 mmHg to a target level of approximately 30–35 mmHg for 4 to 6 hours. Caution is advised when reversing hyperventilation judiciously over 6 to 24 hours to avoid cerebral hyperemia and rebound elevations in ICP secondary to effects of reequilibration (Ropper et al., 2004).

**Osmotherapy Use**

The fundamental goal of osmotherapy is to create an osmotic gradient to cause egress of water from the brain extracellular (and possibly intracellular) compartment into the vasculature, thereby decreasing intracranial volume and improving intracranial elastance and compliance. In healthy individuals, serum osmolality (285–295 mOsm/L) is relatively constant, and the serum Na+ concentration is an estimate of body water osmolality. Under ideal circumstances, serum osmolality is dependent on the major cations (Na+ and K+), plasma glucose, and blood urea nitrogen. Because urea is freely diffusible across cell membranes, serum Na+ and plasma glucose are the major molecules involved in altering serum osmolality (Bhardwaj and Ulatowski, 2004).

The goal of using osmotherapy for cerebral edema associated with brain injury is to maintain a euvolemic or a slightly hypervolemic state. As a fundamental principle, a hypoosmolar state should always be avoided in any patient who has an acute brain injury. A serum osmolality in the range of 300 to 320 mOsm/L has traditionally been recommended for patients with acute brain injury who demonstrate poor intracranial compliance (Ropper et al., 2004).

Chen et al. in 2006 examined the effect of duration of graded increases in serum osmolality with mannitol and hypertonic saline on blood-brain...
barrier disruption and regional cerebral edema in a rat model of large ischemic stroke. They showed that Blood-brain barrier disruption was maximal in rats treated with 0.9% saline for 48 h, but did not correlate with increases in serum osmolality or treatment duration with osmotic agents. Treatment with 7.5% hypertonic saline attenuated water content in the periinfarct regions and all subregions of the contralateral nonischemic hemisphere to a greater extent than mannitol did with no adverse effect on survival rates. These data show that BBB integrity is not affected by the duration and degree of serum osmolality with osmotic agents, and attenuation of increases in brain water content with hypertonic saline to target levels >350 mOsm/L may have therapeutic implications in the treatment of cerebral edema associated with ischemic stroke.

An ideal osmotic agent is one that produces a favorable osmotic gradient, is inert and nontoxic, is excluded from an intact BBB, and has minimal systemic side effects (Bhardwaj and Ulatowski, 2004).

In an experimental ischemic stroke model, the benefits of hypertonic saline in stroke-associated cerebral edema have been studied and reported. For example, in a rat model of transient cerebral ischemia, continuous intravenous infusion of 7.5% NaCl/acetate begun 6 hours after the ischemic insult demonstrated attenuation of water content in the ischemic and non ischemic hemispheres, compared with a bolus of high-dose mannitol (2 gm/kg intravenously every 6 hours) (Toung et al.,2002). Treatment with continuous intravenous infusion of 5 and 7.5% hypertonic saline in a model of permanent focal ischemia attenuated brain and lung water to a greater extent than did mannitol (Toung et al.,2007).

Likewise, intravenous bolus injection of 10% hypertonic saline was shown to be effective in lowering ICP in patients with ischemic stroke
who failed to show such a response to conventional doses of mannitol (Schwarz et al., 2002).

Potential complications concerns with mannitol include hypotension, hemolysis, hyperkalemia, renal insufficiency, and pulmonary edema (Bhardwaj and Ulatowski, 2004).

Myelinolysis, the most serious complication of hypertonic saline therapy, typically occurs when rapid corrections in serum sodium arise from a chronic hyponatremic state to a normonatremic or hypernatremic state. Experimental studies suggest that for myelin injury to occur, the degree of rapid change in serum sodium is much greater from a normonatremic to a hypernatremic state (change of approximately 40 mEq/L) (Harukuni et al., 2002).

Repeated administration of mannitol in the setting of large hemispheric infarction is a controversial and poorly defined therapeutic intervention. Cho et al. in 2007 evaluate the effect of multiple-dose mannitol on a brain edema in a rat model of middle cerebral artery infarction by measuring hemispheric weight and accumulated mannitol in the hemisphere using mannitol dehydrogenase. The study suggests that multiple-dose mannitol is likely to aggravate cerebral edema due to parenchymal accumulation of mannitol in the infarcted brain tissue with increased hemispheric weight of infarction and aggravating brain tissue shift.

Loop Diuretics

The use of loop diuretics for the treatment of cerebral edema, particularly when used alone, remains controversial. Combining furosemide with mannitol produces a profound diuresis; however, the efficacy and optimum duration of this treatment remain unknown (Eccher and Suarez, 2004). If loop diuretics are used, rigorous attention to systemic hydration status is advised, as the risk of serious volume
depletion is substantial and cerebral perfusion may be compromised (Thenuwara et al., 2002).

Acetazolamide, a carbonic anhydrase inhibitor that acts as a weak diuretic and modulates CSF production, does not have a role in cerebral edema that results from acute brain injuries; however, it is frequently used in outpatient practice (Eccher and Suarez, 2004).

Corticosteroid Administration

In ischemic stroke, steroids have failed to show any substantial benefit despite some success in animal models (Poungvarin, 2004).

Decompressive Surgery

The rationale of decompressive surgery is to remove a part of the neurocranium to give space to the swollen brain, thus normalizing ICP, avoid ventricular compression, and prevent brain tissue shifts. Furthermore, by reducing the ICP, cerebral blood flow is facilitated improving the cerebral perfusion pressure (Kohrmann and Schwab, 2009).

Decompressive surgery consists of a large hemicraniectomy and a duraplasty: a large question mark-shaped skin incision based at the ear is made. A bone flap with a diameter of at least 12 cm (including the frontal, parietal, temporal, and parts of the occipital squama) is removed. Additional temporal bone is removed so that the floor of the middle cerebral fossa can be explored. Then the dura is opened and an augmented dural patch, consisting of either homologous periost or temporal fascia or both, is inserted (the size may vary, usually a patch of 15–20 cm in length and 2.5–3.5 cm in width is used). The dura is fixed at the margin of the craniotomy to prevent epidural bleeding. The temporal muscle and the skin flap are then reapproximated and secured. Ischemic brain tissue usually is not resected. During this procedure, also an ICP
probe can easily be inserted for further monitoring. In surviving patients, cranioplasty is performed after at least 6 weeks (usually 3–6 months), using the stored bone flap or an artificial bone flap (Robertson et al., 2004).

From a clinical point of view, it is unclear which factors promote early and rapid brain swelling, or which factors are protective making an early prognosis is problematic (Hofmeijer et al., 2008). Mori et al. in 2004 retrospectively compared patients, who had been treated before the onset of brain herniation, with those who showed clinical and radiological signs of herniation. Mortality was markedly reduced from 17.2 to 4.8% after 1 month and from 27.6 to 19.1% after 6 months, respectively. Outcome at 6 months was also significantly improved by early intervention.

In the lack of trials truly testing early vs. delayed intervention, early hemicraniectomy is recommended based on available results from DESTINY and DECIMAL which both performed early surgery (within 36 h and 30 h, respectively) (Vahedi et al., 2007) (Juttler et al., 2007).
Recommendations

Priority Aims

1. Increase the percentage of patients presenting within the window of thrombolytic therapy administration.
2. Increase the percentage of patients presenting with TIA symptoms within 24 hours at high risk for stroke who are admitted to hospital.
3. Increase the percentage of non-tPA recipients who have hypertension appropriately managed in the first 48 hours of hospitalization or until neurologically stable.
4. Increase the percentage of patients who receive appropriate medical management for prevention of complications within the initial 24-48 hours of diagnosis.
5. Improve patient and family education of patients with ischemic stroke in both the ED and the admitting hospital unit.

Public awareness and Education

Recommendations

• Educational programmes to increase awareness of stroke at the population level are recommended.

• Educational programmes to increase stroke awareness among professionals (paramedics/emergency physicians) are recommended.

The “time is brain” concept means that treatment of stroke should be considered as an emergency. Thus, avoiding delay should be the major aim in the prehospital phase of acute stroke care. This has far-reaching implications in terms of recognition of signs and symptoms of stroke by the patient or by relatives or bystanders, the nature of first medical contact, and the means of transportation to hospital.
Referral and patient transfer

Recommendations

• Immediate emergency medical service (EMS) contact and priority EMS dispatch are recommended.
• Priority transport with advance notification to the receiving hospital is recommended.
• It is recommended that suspected stroke victims should be transported without delay to the nearest medical centre with a stroke unit that can provide ultra-early treatment.
• Immediate emergency room triage, clinical, laboratory and imaging evaluation, accurate diagnosis, therapeutic decision and administration of appropriate treatments at the receiving hospital are recommended.
• It is recommended that in remote or rural areas telemedicine should be considered in order to improve access to treatment.
• It is recommended that patients with suspected TIA be referred without delay to a TIA clinic or to a medical centre with a stroke unit that can provide expert evaluation and immediate treatment.

Emergency management

Recommendations

• Organization of pre-hospital and in-hospital pathways and systems for acute stroke patients is recommended.
• Ancillary tests are recommended.

Stroke services and stroke units

Recommendations

• It is recommended that all stroke patients should be treated in a stroke unit.
• It is recommended that healthcare systems ensure that acute stroke patients have access to high technology medical and surgical stroke care when required.
• The development of clinical networks, including telemedicine, is recommended to expand access to high technology specialist stroke care.

Diagnostic imaging
Recommendations
• In patients with suspected TIA or stroke, urgent cranial CT, or alternatively MRI, is recommended.
• If MRI is used, the inclusion of diffusion weighted imaging (DWI) and T2*-weighted gradient echo sequences is recommended.
• In patients with TIA, minor stroke or early spontaneous recovery immediate diagnostic work-up, including urgent vascular imaging (ultrasound, CT-angiography, or MR angiography) is recommended.

Other diagnostic tests
Recommendations
• In patients with acute stroke and TIA, early clinical evaluation, including physiological parameters and routine blood tests, is recommended.
• It is recommended that all acute stroke and TIA patients should have a 12-lead ECG. In addition continuous ECG recording is recommended for ischaemic stroke and TIA patients.

General stroke treatment
Recommendations
• Intermittent monitoring of neurological status, pulse, blood pressure, temperature and oxygen saturation is recommended for 72 hours in patients with significant persisting neurological deficits.
• It is recommended that oxygen should be administered if the oxygen saturation falls below 95%.
• Regular monitoring of fluid balance and electrolytes is recommended in patients with severe stroke or swallowing problems.
• Routine blood pressure lowering is not recommended following acute stroke.
• It is recommended that abrupt blood pressure lowering be avoided.
• Monitoring serum glucose levels is recommended.
• Treatment of serum glucose levels >180 mg/dl with insulin titration is recommended.
• It is recommended that severe hypoglycaemia (<50 mg/dl) should be treated with intravenous dextrose or infusion of 10–20% glucose.
• It is recommended that the presence of pyrexia should prompt a search for concurrent infection.
• Treatment of pyrexia with paracetamol and fanning is recommended.

Specific treatment
Recommendations
• Intravenous rtPA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 4.5 hours of onset of ischaemic stroke, although treatment between 3 and 4.5 h is currently not approved by FDA.
• The use of multimodal imaging criteria may be useful for patient selection for thrombolysis but is not recommended for routine clinical practice.
• It is recommended that blood pressures of 185/110 mmHg or higher is lowered before thrombolysis.
• Intra-arterial treatment of acute MCA occlusion within a 6-hour time window is recommended as an option.
• Intra-arterial thrombolysis is recommended for acute basilar occlusion in selected patients. Intravenous thrombolysis for basilar occlusion is an acceptable alternative even after 3 hours.

• It is recommended that if thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 hours.

• Currently, there is no recommendation to treat ischaemic stroke patients with neuroprotective substances.

Brain oedema and elevated intracranial pressure
Recommendations

• Surgical decompressive therapy within 48 hours after symptom onset is recommended in patients up to 60 years of age with evolving malignant MCA infarcts.

• It is recommended that osmotherapy can be used to treat elevated intracranial pressure prior to surgery if this is considered.

• It is recommended that ventriculostomy or surgical decompression be considered for treatment of large cerebellar infarctions that compress the brainstem.

Prevention and management of complications
Recommendations

• It is recommended that infections after stroke should be treated with appropriate antibiotics.

• Prophylactic administration of antibiotics is not recommended, and levofloxacin can be detrimental in acute stroke patients.

• Early rehydration and graded compression stockings are recommended to reduce the incidence of venous thromboembolism.

• Early mobilization is recommended to prevent complications such as aspiration pneumonia, DVT and pressure ulcers.
• It is recommended that low-dose subcutaneous heparin or low molecular weight heparins should be considered for patients at high risk of DVT or pulmonary embolism.
• Administration of anticonvulsants is recommended to prevent recurrent post-stroke seizures. Prophylactic administration of anticonvulsants to patients with recent stroke who have not had seizures is not recommended.
• An assessment of falls risk is recommended for every stroke patient.
• In stroke patients with urinary incontinence, specialist assessment and management is recommended.
• Early commencement of nasogastric feeding is recommended in stroke patients with impaired swallowing.
Algorithm For Hyperacute Stroke Management

(Bader and Palmer, 2006)

Patient presents with weakness/numbness arm/leg/face, facial droop, difficulty with speech, loss of speech, slurred speech, difficulty swallowing, ataxia, nystagmus, dysconjugate gaze, vomiting, facial weakness, absence of gag/swallow reflex, dysarthria, dysphagia, severe headache, decrease LOC, unexplained nausea/vomiting

1:0 personnel assess patient, obtain vital sign/neuro checks, monitor ECG/pulse ox, start IV, and draw blood
RN perform abbreviated NIHSS, notify ED MD (perform complete NIHSS)

Time of symptom onset determined

Greater than 6 hours
Obtain CT scan of brain ASAP

Less than 6 hours
Call 911, announce code stroke, and call code stroke team
Notify neuroradiologist/interventional radiologist on call
Stat CT scan of brain obtained within 25 minutes of arrival

No hemorrhage
Review inclusion/exclusion tPA or Merci retrieval

Decision tree

Hemorrhage on CT
Go to Hemorrhagic Algorithm

No tPA or tPA indicated due to exclusions or patient improves

Pt refuses tPA or No tPA indicated due to exclusions or patient improves

Less than 3 hours
Intravenous tPA
Informed consent
MD orders ED IV tPA
Dose: 0.9 mg/kg IV given over 60 minutes per protocol
Admit to Stroke Unit
Complete acute ischemic order set

Less than 6 hours
Interventional procedure
IV/IA tPA, IA tPA, Merci device
Informed consent

IV/IA
IA
Merci retrieval
Dose 0.6 mg/kg IV over 30 min in ED
Pt transferred to Interventional
Cerebral angiogram:
tPA/Merci retrieval as indicated
REFERENCES


-100-


-**Bershad EM, Suarez JI.** Recent advances in intra-arterial thrombolysis. Ann Indian Acad Neurol 2008;11:30-38.


-Poungvarin N. Steroids have no role in stroke therapy. Stroke 2004;35:2229–2230.


-116-


-Von Kummer R. Early major ischemic changes on computed tomography should preclude use of tissue plasminogen activator. Stroke.2003; 34: 820–821.


