Doi: 10.32481/djph.2023.08.006

Medical Management of Acute Cerebral Ischemia

Usman Shehzad, MD

Vascular Neurologist, Bayhealth Medical Center; Chair, Stroke System of Care, Delaware

Abstract

This review article discusses medical management of acute cerebral ischemia including recent advances. Expansion of the thrombolysis eligibility criteria are discussed. Tenecteplase as a promising new thrombolytic is explored and the evidence supporting the use of Mobile Stroke Units is presented.

Introduction

Stroke remains a leading cause of serious long-term disability in the United States, with more than 795,000 individuals suffering from a stroke every year.[1] More than 160,000 deaths occur annually with stroke as the underlying cause and in 2020, stroke was responsible for approximately 1 out of 21 deaths in the nation.[1] Within Delaware, 3135 strokes were reported in the calendar year 2022.[2] While the term stroke encompasses both hemorrhagic and acute ischemic strokes (AIS), the latter is the most common stroke type accounting for 87% of all strokes.[1] For the purpose of this review, stroke is used interchangeably with AIS. It must be noted that tremendous leaps have been made in the interventional/surgical management of AIS and are discussed elsewhere in this issue. This review will focus on the medical management of acute cerebral ischemia.

Hyperacute Assessment of Stroke Patients

Optimal management of stroke requires efficient delivery of care starting from the moment a patient recognizes their stroke symptoms and contacts Emergency Medical Services (EMS). Routing of the patient to a correct medical facility is of critical importance and is discussed in the stroke systems of care article published in this issue. Upon arriving at the emergency room (ER), multidisciplinary care is required to ensure there are no delays in the delivery of care to these patients as early treatment is shown to result in the best outcomes possible.[3] Many events need to occur in parallel on patient arrival as initially their airway, breathing and circulation (ABCs) are assessed. A focused physical examination, as well as obtaining the National Institute of Health Stroke Scale (NIHSS), occurs as the patient is being rushed to the CT scanner for head and neck imaging. Review of imaging, focused history taking, and obtaining collateral information need to occur simultaneously as the nursing staff draws blood, obtains intravenous (IV) access, weighs the patient, records an EKG, connects the patient to telemetry monitoring, etc. Given the complexity of assessment and the need for efficiency, the American Heart Association (AHA) Stroke guidelines recommend an organized protocol for the emergency evaluation of patients with suspected stroke, as well as designation of an acute stroke team that includes physicians, nurses, and laboratory/radiology personnel.[3]

The phrase “time is brain” was coined by Dr. Camilo R. Gomez in 1993 to signify the importance of timely intervention in stroke management[4] and in 2005, Dr. Jeffrey Saver provided quantification of this concept by showing that a typical stroke patient loses 1.9 million

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neurons each minute in which stroke is left untreated.[5] Therefore, optimizing stroke pathways must be made a high priority for any healthcare system providing acute stroke treatment.

Early review and management of vital signs, EKG changes, and laboratory abnormalities play an important role in the assessment of acute stroke patients. Allowing for permissive hypertension is the norm, though it is not known what blood pressure range produces the best outcome for stroke patients, and these decisions should be made on a case-by-case basis. Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support vital organs. For patients that are eligible for thrombolysis, the blood pressure should be <185 mm Hg systolic and <110 mm Hg diastolic. Hypoglycemia (blood glucose < 60 mg/dL) should be corrected in patients presenting with stroke symptoms. Of note, in patients that are eligible for thrombolysis, finger stick glucose is the only lab work that is required prior to thrombolytic administration, unless the patient has a known condition necessitating blood work such as underlying coagulopathy, thrombocytopenia, etc.[3]

Head positioning, particularly the benefits of laying flat as opposed to elevated head positioning, are not well studied. A single large trial studying this practice found no difference in outcome for patients with flat head positioning vs. elevated head positioning. The trial had many limitations, but importantly concluded that there was no increase in risk of aspiration pneumonia with flat head positioning.[6] Thus, this decision should also be made on a case-by-case basis.

Intravenous Thrombolysis

tPA Development and Initial Approval

IV thrombolysis was first reported in literature in 1958 when Drs. Sussman and Fitch published a case series of three patients treated with IV infusion of fibrinolysin.[7] Trials testing different candidates for thrombolysis became more frequent in the 1980s with urokinase and streptokinase being the most widely studied drugs. In 1991, mass production of recombinant tissue plasminogen activator (tPA) began.[8] tPA is a naturally occurring protease that lyses blood clots by attaching to fibrin found on the surface of the clot and activation of plasminogen, which in turn produces plasmin leading to clot lysis . Recombinant technology has allowed for the creation of modified versions of tPA, such as alteplase, reteplase, and tenecteplase. These modified versions of tPA have slightly different properties, such as their ability to bind to fibrin and their half-life.[9] Alteplase was the first modified version of tPA to be studied.

The National Institute of Neurological Disorders and Stroke (NINDS) published a landmark trial in 1995 that showed the effectiveness of alteplase for the treatment of acute ischemic stroke in patients who were able to be treated within 180 minutes of their last known well time.[10] The trial had two parts:

- Part 1 tested whether alteplase was more effective than placebo at improving the NIHSS score at 24 hours. The NIHSS is a scale that measures the severity of stroke symptoms.
- Part 2 tested whether alteplase was more effective than placebo at improving clinical outcomes at three months. Clinical outcomes were measured using the Berthel Index, modified Rankin Scale (mRS) (Table 1), Glasgow Outcome Scale, and NIHSS.

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Part 1 of the trial did not show a significant difference between alteplase and placebo. However, Part 2 of the trial showed that alteplase was more effective than placebo at improving clinical outcomes at three months. The global odds ratio for a favorable outcome including mRS score of 0 or 1 was 1.7, meaning that patients who received alteplase were 70% more likely to have a favorable outcome than patients who received placebo (Figure 1).

The administration of alteplase did result in an increased risk of symptomatic intracranial hemorrhage (sICH). The incidence of sICH was 6% in the alteplase arm as compared to 0.6% in the placebo arm. The study authors concluded that "despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous alteplase within three hours of the onset of ischemic stroke improved clinical outcome at three months." The results of this trial led to the ultimate approval by the Food and Drug Administration (FDA) of alteplase for use in acute ischemic strokes within 180 minutes of last known well in March 1996.[11]

Table 1. Modified Rankin Scale (mRS) Score, a Scale to Assess the Degree of Disability after Stroke

Score	Description
0	The patient has no residual symptoms.
1	The patient has no significant disability; able to carry out all pre-stroke activities.
2	The patient has slight disability; unable to carry out all pre-stroke activities but able to look after self without daily help
3	The patient has moderate disability; requiring some external help but able to walk without the assistance of another individual
4	The patient has moderately severe disability; unable to walk or attend to bodily functions without assistance of another individual
5	The patient has severe disability; bedridden, incontinent, requires continuous care
6	The Patient has expired

Figure 1. Modified Rankin Scale Score Distribution at 90 Days for Patients Treated with Alteplase Compared to Placebo for Acute Ischemic Stroke. Image created using data from the NINDS tPA trial[10]

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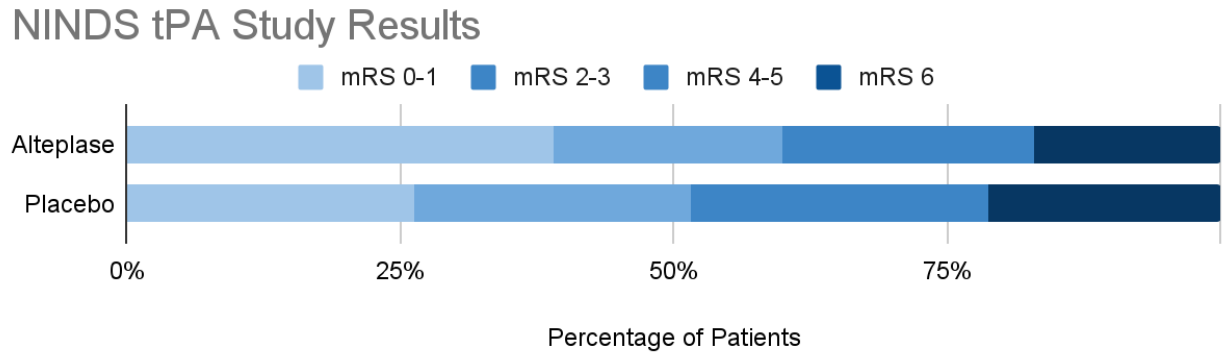

The European Cooperative Acute Stroke Study (ECASS) III trial was published in September 2008.[12] This trial tested the efficacy of alteplase compared to placebo in patients treated 3-4.5 hours from their last known well times. The primary endpoint of the study was disability at 90 days, as measured by the mRS (Table 1). A favorable outcome was defined as an mRS score of 0 or 1. The odds ratio for a favorable outcome with alteplase was 1.28 compared to placebo. The incidence of sICH was higher with alteplase than with placebo. In this trial, 2.4% of patients who received alteplase experienced sICH, compared to 0.2% of patients who received placebo. The results of the ECASS III trial suggest that alteplase can be an effective treatment for acute ischemic stroke when given within 3-4.5 hours of the last known well time. While the FDA has not approved alteplase in the 3-4.5 hour time window, several organizations, including the American Heart Association/American Stroke Association have recommended using it in this time frame.[3]

Given the significant risks of hemorrhage associated with alteplase use, it is of critical importance to be familiar with the exclusion criteria for IV thrombolysis. The initial alteplase contraindications strictly adhered to the exclusion criteria in the above-mentioned trials. Over time, these exclusion criteria have become less restrictive as more evidence has shown favorable risk-to-benefit profiles in some of the situations where alteplase administration was previously an absolute contraindication. As an example, patients who had seizure at the onset of stroke were excluded from the NINDS trial and stroke guidelines that were published in 1996 recommended against giving alteplase in this scenario.[13] Whereas, the most recent stroke guidelines state “IV alteplase is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon.”[3] It is important to note that despite an increase in utilization of IV thrombolysis, reported incidence of sICH from alteplase use in recent studies is much lower than the NINDS trial summarized above.[14]

Extending the tPA Window

In addition to the exclusion criteria becoming less restrictive, there has been an effort to safely expand thrombolysis eligibility by using what is referred to as the “tissue window” in patients that cannot be treated using the “time window.” It was hypothesized that advanced imaging parameters can be used to determine eligibility for thrombolysis in patients presenting with stroke symptoms outside of the 4.5-hour time window. The research supporting this concept culminated in the publication of two trials discussed next.

In 2018, Thomella and colleagues published the WAKE-UP trial[15] in which they used Magnetic Resonance Imaging (MRI) to guide treatment. While a detailed discussion on MRI sequences is

beyond the scope of this article, Figure 2 provides a brief overview of MRI sequences relevant to this research. WAKE-UP trial investigators selected patients with a large DWI signal (tissue at risk of infarction) who had little or no FLAIR signal (already infarcted tissue) and randomized them to receive alteplase or placebo. This trial showed that patients who received alteplase based on the imaging criteria were more likely to have an MRS of 0 or 1 compared to placebo with the odds ratio of 1.61. Death or dependency at 90 days was numerically higher in the placebo group (18.3% vs 13.5%); death at 90 days was numerically higher in the alteplase group (4.1% vs 1.2%) but neither of these reached statistical significance. Rate of sICH was numerically higher in the alteplase group (2% vs 0.4%), however, this did not reach statistical significance either.

Figure 2. A Brief Description of Select MRI Sequences

A Brief Description of Select MRI Sequences

Imaging Sequence	Brief Description
Diffusion Weighted Imaging (DWI)	Increased DWI signal is seen within minutes of an arterial occlusion and reflects a combination of infarcted brain and reversible ischemic tissue.[1]
Fluid Attenuated Inversion Recovery (FLAIR)	Abnormal (hyperintense) FLAIR signal is usually indicative of irreversible cerebral ischemia (completed stroke).[2]
Gradient Recalled Echo (GRE)*	Abnormal GRE signal may indicate presence of hemorrhage.[3]
Susceptibility Weighted Imaging (SWI)*	Abnormal SWI signal may indicate presence of hemorrhage.[4]
Perfusion Weighted Imaging (PWI)	PWI provides information about hemodynamic parameters such as cerebral blood volume, cerebral blood flow and transit time.[5]

* typically, an MRI would include either GRE or SWI sequences

1. Tozer Fink, K., & Fink, J. (2018). *Principles of Neurosurgery* (4th ed.). Elsevier Inc.
2. Meshksar, A., et al. (2014). *AJNR*, *35*(5), 878–883
3. Tang, M. Y., et al. (2014). *BioMed research international*, *2014*, 312142.
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In 2019 Ma and colleagues published the EXTEND trial[16] in which MRI or Computed Tomography Perfusion (CTP) scans were used to determine patient eligibility for thrombolysis. CTP is an imaging technique in which IV iodinated contrast bolus is administered and rapid sequential scans are obtained to assess the blood perfusion status of the brain parenchyma, pertinent sequences are described in Figure 3. Similar in concept to the DWI/FLAIR discussion above, if the CTP showed a mismatch between Tmax > 6 seconds and CBF < 30%, the patient was eligible for enrollment in the trial. The EXTEND trial also concluded that patients who received alteplase using imaging criteria were more likely to have minimal or no disability (mRS 0 or 1) at 90 days with an adjusted risk ratio of 1.44 compared to placebo. Death within 90 days and rates of sICH were numerically higher in the alteplase group, but this did not reach statistical significance.

Figure 3. A Brief Description of Select CTP Sequences

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A Brief Description of Select CTP Sequences	
Imaging Sequence	Brief Description
Time to Maximum (Tmax)	This is the time it takes for the contrast dye to reach its maximum concentration in an area of the brain. Tmax > 6 seconds is considered to be tissue at risk of infarction.
Cerebral Blood Flow (CBF)	This is the amount of blood flowing through an area of the brain per unit of time. CBF < 30% is considered to be irreversibly infarcted tissue.
Cerebral Blood Volume (CBV)	This is the amount of blood that is contained in an area of the brain.

Created using information from Li, K., et al. (2019). *Medical physics*, *46*(11), 4869–4880.

Based on the WAKE-UP trial, the AHA added a Level IIa recommendation supporting the use of alteplase in patients selected using MRI guidance[3]; the EXTEND trial results did not get released in time for consideration by the guidelines committee.

Acute Treatment of Mild Non-Disabling Stroke

In 2016, Messé and colleagues used the Get With the Guidelines registry to determine common causes for otherwise eligible patients to not receive IV alteplase.[17] "Rapid improvement or mild stroke" was most commonly documented as a cause for withholding alteplase, sighted in 51.4% of the cases. At the time, the AHA stroke guidelines indicated uncertainty regarding using alteplase in patients with low NIHSS scores and non-disabling deficits. This was only a Class IIB (weak) recommendation with quality of evidence level C-LD (limited data).[18]

This led to the design of the PRISMS trial in which investigators sought to test efficacy and safety of alteplase in suspected stroke patients who presented with minor deficits.[19] Patients were enrolled if they had an NIHSS score ≤ 5 and a mild non-disabling deficit. The determination of non-disabling was made in consultation with the patients and available family members. Patients were randomized to receive alteplase or aspirin 325 mg, and the primary outcome was mRS score of 0 or 1 at 90 days. Alteplase was not shown to increase the likelihood of favorable functional outcome at 90 days in this study.

The more recently published ARAMIS trial was designed to investigate whether dual antiplatelet therapy (DAPT) was non-inferior to alteplase in patients presenting with minor non-disabling strokes.[20] DAPT in this trial was defined as aspirin 100 mg daily as well as clopidogrel 300 mg on day 1 followed by 75 mg daily. Eligible patients were randomized to be treated with either alteplase or DAPT and the primary endpoint was excellent functional outcome (defined as mRS score of 0 or 1) at 90 days. The study succeeded in showing that DAPT is non-inferior to alteplase in achieving excellent functional outcome at 90 days in patients presenting with minor, non-disabling strokes.

The most recent AHA guidelines added a new recommendation stating that for otherwise eligible patients with mild non-disabling stroke symptoms, alteplase is not recommended.[3] Since what constitutes disabling is a subjective matter, it is prudent to include the patient and their family in determining severity of their presenting symptoms.

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Tenecteplase for Thrombolysis in Acute Stroke

Tenecteplase is a genetically modified variant of alteplase optimized to have increased fibrin specificity. Additionally, tenecteplase has a longer half-life than alteplase, meaning it can be given as a single injection whereas alteplase must be given as a bolus followed by an infusion. The latest AHA stroke guidelines state that "tenecteplase might be considered as an alternative to alteplase in patients with minor neurological impairments and no major intracranial occlusions."[3] However, these guidelines predate the release of recent compelling data supporting the use of tenecteplase.

The larger early trials testing efficacy of tenecteplase were included in a meta-analysis by Drs. Burgos and Saver.[21] The meta-analysis included five randomized trials enrolling 1585 patients. As there was not an established therapeutic dose of tenecteplase, there was a variety of doses used in these five trials. The primary outcome of this meta-analysis was a mRS score of 0 or 1 after 90 days. This endpoint was reached in 57.9% of the patients treated with tenecteplase and 55.4% of the patients treated with alteplase. The authors concluded that tenecteplase was non-inferior to alteplase for the treatment of acute ischemic stroke. Subgroup analysis looking at the doses tested showed that only the patients treated with 0.25 mg/kg and 0.4 mg/kg doses met the primary outcome.

Two recent trials have provided more information regarding tenecteplase dosing. The AcT trial was a non-inferiority trial in which patients eligible for thrombolysis were randomly assigned to receive either the standard dose of alteplase or tenecteplase 0.25 mg/kg.[22] This trial showed that 0.25 mg/kg dose of tenecteplase "is a reasonable alternative to alteplase for all patients presenting with acute ischemic stroke who meet standard criteria for thrombolysis."

NOR-TEST 2 was a non-inferiority trial in which patients eligible for thrombolysis received either standard dose of alteplase or 0.4 mg/kg dose of tenecteplase.[23] The trial was stopped early for safety reasons and showed that "tenecteplase at a dose of 0.4 mg/kg yielded worse safety and functional outcomes compared with alteplase." Thus, the current practice in most centers is to use 0.25 mg/kg dose of tenecteplase.

One subgroup of stroke patients in which tenecteplase has been shown to be superior to alteplase are the patients that are eligible for both IV thrombolysis and mechanical thrombectomy. The EXTEND-IA TNK trial enrolled such patients and randomized them to receive standard dose of alteplase or 0.25 mg/kg dose of tenecteplase.[24] Patients in the tenecteplase arm were twice as likely to have substantial reperfusion before thrombectomy (22% vs 10%). Additionally, secondary analysis showed that the median mRS at 90 days for tenecteplase treated patients was 2 compared to a median mRS of 3 for the alteplase treated group. This has led to a level IIb recommendation by the AHA that it may be reasonable to choose tenecteplase over alteplase in patients who are also eligible to undergo mechanical thrombectomy.[3]

Patients Outside the TPA Window

While the importance of thrombolysis cannot be overstated, it is important to recognize that almost 90% of the patients that present to the hospital with stroke symptoms are not candidates for IV thrombolysis.[9] Early treatment for these patients starts with the initial evaluation and correction of blood glucose, blood pressure, and other measures outlined above.

Early antiplatelet therapy (initiated within 48 hours) with aspirin[25,26] or clopidogrel[27] has been shown to be beneficial for patients presenting with acute ischemic stroke. In patients presenting with mild stroke symptoms, a limited course of dual antiplatelet therapy with aspirin and clopidogrel was shown to be superior to single antiplatelet therapy in the CHANCE and POINT trials.[28,29] Mild strokes in these trials were defined as those patients that presented with NIHSS ≤ 3 or those with high risk Transient Ischemic Attack (TIA) defined as $ABCD_2$ score of ≥ 4. $ABCD_2$ is a score that takes into account the patient's age, blood pressure, clinical features, duration, and presence of diabetes to stratify patients into low, medium or high risk for recurrence of stroke. While both of these trials administered DAPT for different durations, a meta-analysis of these two trials showed that the benefit of DAPT was confined to the first 21 days after the minor stroke or high-risk TIA.[30] Thus in patients with mild ischemic strokes or high risk TIAs, a 21-day course of DAPT should be used unless contraindicated.

Other than these initial management decisions, a thorough investigation into determining the stroke etiology is critical. While it may be over simplified, the TOAST trial's classification of stroke subtypes is a good starting point.[31] TOAST categorized stroke etiology into the following five categories: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology. Once a stroke is categorized into one of these general categories, risk factors specific to the individual patient can be identified and treated appropriately based on best evidence.

Mobile Stroke Unit

As emphasized throughout this article, timely stroke care is of the utmost importance to ensure best outcomes for patients. In addition to optimizing stroke care after a patient's arrival to the emergency room, a Mobile Stroke Unit (MSU) can bring the "emergency room" to the patient. The concept of MSU was introduced by Dr. Fassbender and colleagues in 2003.[32] They proposed designing a vehicle capable of carrying all the relevant personnel, equipment and diagnostic tools (including a CT scanner) required for safe administration of IV thrombolysis in the field prior to bringing the patient to the ER. Since then, this proposed vehicle has been developed, deployed and studied extensively. A meta-analysis of the published studies comparing MSU and conventional stroke treatment showed that compared with usual care, MSU use was associated with a 30 minute reduction in stroke onset to IV thrombolysis administration and a 65% increase in the odds of excellent outcome (mRS 0 or 1 at 90 days).[33] While implementation of an MSU is a costly undertaking, studies have shown MSU use to be cost effective considering internationally accepted thresholds and associated with higher quality adjusted life years (QALY)[34–36]

Future Directions

The past decade has seen an increase in the speed of evolution of stroke care as interventional management of stroke, improvements in medical management as well as improvement in stroke rehabilitation has led to overall declines in death and Disability Adjusted Life-Years (DALY) resulting from stroke.[37] There are ongoing studies looking to expand the inclusion criteria for IV thrombolysis even further such as in the patients taking direct oral anticoagulants.[38] Other studies are evaluating the combination of IV antiplatelets such as eptifibatide and argatroban with thrombolysis to improve reperfusion.[39] Mobile Stroke Units have the potential to significantly improve outcomes for stroke patients. However, there are financial (appropriate reimbursement)

and logistical challenges (development of optimal deployment protocols in different geographical locations) that need to be addressed before mobile stroke units can be widely implemented. Combining acute stroke treatment with neuroprotection has thus far been unsuccessful however the advent of endovascular therapies has brought renewed interest in this field.[40]

Conclusion

In patients presenting with acute ischemic stroke, rapid evaluation and efficient decision making is of utmost importance to improve patient outcomes. Expansion in the thrombolysis eligibility criteria by elimination of some previous contraindications and development of new selection criteria in the extended time window has allowed for more patients to be treated with IV thrombolysis. Furthermore, the advent of Mobile Stroke Units has brought a new paradigm to the treatment of AIS patients.

Dr. Shehzad may be contacted at usman_shehzad@bayhealth.org.

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