https://doi.org/ 10.33472/AFJBS.6.4.2024.452-472

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Etiology and conduct of Stroke: Current status and Impending Prospectives

Swikriti[1], Lovish Chhabra[2], Shilpi Arora[3], Hemlata Sharma[1], Sukhpreet Singh[5] , Shakshi Kumari[4], Rajeshwari Kumari [4], Deepika barnwal[4]

1, Faculty of Pharmacy, Swami Vivekanand College of Pharmacy, Banur, Punjab , India.

2, Chitkara College of Pharmacy, Chitkara University, Punjab,India.

3,Faculty of Pharmacy, Himachal Institute of Pharmacy, Paonta Sahib, H.P. India.

4, Swami Vivekanand College of Pharmacy, Banur, Punjab , India.

5, Faculty of Pharmacy, GNA School of Pharmacy, GNA University,Phagwara , India.

Corresponding Author

Swikriti

Associate Professor Swami Vivekanand College of Pharmacy, Banur, Punjab

Email: swikritisharma77@gmail.com

Article History
Volume 6,Issue 4, Feb 2024
Received:17 Feb 2024
Accepted : 01 Mar 2024
doi: 10.33472/AFJBS.6.4.2024.452-472

ABSTRACT

Stroke is a neurological condition which is a grave condition or often fatal. It is the second leading cause of mortality and impairment. It is a disease in which brain do not get sufficient amount of oxygen and blood because of blockage of blood vessel. Stroke is not only caused by a single disease but it can also be triggered by multiple numbers of risk factors like age, hypertension, hyperlipidemia, atrial fibrillation etc. Most of the hypertension patients may also suffers from stroke. Unfortunately, there is currently no direct or simple treatment present for stroke. As it can only be treated by modifying the risk factor. Tissue plasminogen activator is a modern technique which is used for treating the stroke. In this treatment, a naturally occurring protein play the most important role in the breakdown of blood clots by formation of plasmin by plasminogen bridging the gap between preclinical and clinical studies is essential, by following guidelines like stair and improve. Emerging treatments like tissue plasminogen activator, mechanical thrombolysis and neuroprotectant peptides shows commitment but it also required further research.

KEYWORDS: - Stroke, Tissue plasminogen activator, risk factors, blood clot, reperfusion, thrombolysis

INTRODUCTION

Stroke is a prevalent disorder that is fatal in nature. It is the second-ranked cause of mortality and impairment, affecting human well-being [1]. It's a neurological condition in which the brain does not receive sufficient oxygen according to its needs [2]. Globally, it is the foremost reason for adult impairment and also the fifth foremost reason for mortality [3]. Stroke, a cerebrovascular incident, appears due to brain ischemia, indicating inadequate blood supply to the brain, resulting in tissue transformation [4]. The major cause of ailment and death worldwide, including a considerable strain on different areas and healthcare systems. Most strokes are ischemic and are caused by blocked arteries in the brain, leading to inadequate blood flow and potential brain damage [5]. These changes or damages in brain tissues result in stroke or brain infarction. Despite ongoing research, there's an inadequacy of effective medications permitted for protecting the brain during a stroke [6]. Also, a survey conducted up to 2010 revealed that around 16.9 million individuals' acquaintance a stroke annually, cementing its status as an easily seen contributor to global mortality and disability. This leads to the critical need for better treatment to advance results for stroke patients [7].

In recent research, it's found that the use of natural products has become progressively central in the inquiry for effective treatments for ischemic stroke. These compounds show rising neuroprotective properties in experimental studies considering their critical role in the evolution of new therapies. Consequently, harnessing phytochemicals for treatment holds considerable clinical importance in encouraging outcomes for respective affected by an ischemic stroke [8].

Stroke is a major health issue with various types, which include bleeding in the brain and also shows blockages in blood vessels [2]. Stroke is generally classified into two types: hemorrhagic stroke and ischemic stroke [9] Hemorrhagic stroke is expressed by bleeding into the brain or subarachnoid space as a result of blood vessel rupture and gives significant morbidity and mortality rates which is responsible for severe health consequences and often leading to death. This type of stroke causes diverse challenges for patients and healthcare providers due to its devastating shock on neurological function and comprehensive well-being. The worst part of hemorrhagic stroke over time is that it leads to increasingly drastic outcomes. With time the recognition and intervention are crucial due to the emblematic rapid growth of the hemorrhage, resulting in abrupt declines in consciousness and neurological function. Early recognition and management are vitally important to alleviate the disastrous consequences of hemorrhagic stroke, as its growth may lead to swift deterioration and increase neurological impairments [10]

Globally, incidents of hemorrhagic stroke are reported in up to 15% to 25% of stroke cases. In a ratio of the population, it seems that the cases in men are more prevalent with age. In the worldwide development of hemorrhagic stroke, the hype, especially in Asian and African nations, stipulates the drifting of increasing cases.

Hemorrhagic stroke occurs more frequently in men and becomes more prevalent with advancing age. The worldwide occurrence of this type of stroke is on the rise, particularly in African and Asian nations, indicating a concerning trend of increasing incidence in these regions.[11][10][12] Ischemic stroke occurs due to blood clot formation, obstruction of blood vessels, and hypotension. The process of clot formation is also known as thrombosis, wherein

there is a blockage in the blood vessel or vascular occlusion. Hypotension occurs due to the lowering of arterial pressure [13]. Ischemic stroke leads to tissue decay and programmed cell death through various mechanisms such as the inflammatory response, acidic tissue conditions, and neuronal overstimulation [14].

Cerebral ischemia is classified into two categories:

A. Global ischemia: This occurs when there is diminished blood circulation in the brain due to heart failure. It happens because of a decrease in the systemic circulation, which leads to a deficiency of oxygen and glucose in the brain [15]
B. Focal ischemia: This occurs due to a decrease in systemic circulation in the central region of the brain. A decrease in systemic circulation results in a decline in ATP and also causes cerebral infarction in the brain [16].

The brain requires a continuous supply of blood. The blood flow should vary between 50-60 ml per 100 grams per minute. Neural function ceases temporarily if the blood supply decreases to 10-20 ml per 100 grams per minute. Normal blood flow is restored only when circulation resumes. If blood perfusion drops below 10 ml per 100 grams per minute, it results in neural and brain cell apoptosis [17;18]. An auxiliary vascular channel originating from the cervical and spinal regions in the neck is responsible for persistent blood supply to the brain [19]. Arteries like the carotid artery and vertebral arteries merge at a point known as the Circle of Willis [20]. The Circle of Willis ensures adequate blood supply to the brain, even in the presence of a blockage in one of the main arteries [19].

Cerebral stroke, also known as a cerebrovascular accident (CVA), is the primary cause of cerebral injury due to the sudden bursting of brain arteries. Typically, patients affected by cerebral stroke are over 40 years old, with men being more affected than women, and in extreme cases, it can lead to mortality [21]. The main challenge of cerebrovascular accidents lies in their causes, such as an increase in mortality rates and the often-accompanying impairments [22,23] Present therapies remain insufficient in demonstrating their full effectiveness on cerebral stroke; thus, prevention remains the most effective approach.

It has been observed that patients suffering from undernourishment and excessive weight may also experience strokes, leading to complicated recovery journeys. Several reviews [24] have shown a significant incidence of undernourishment (ranging between 8.2% to 49%) and dysphagia (ranging between 24.3% to 52.6%) in cardiovascular accident patients. Some research [25] has also linked low plasma albumin concentration to reduced grip strength in stroke patients, which is often attributed to malnutrition.

A recent study [26,27] has highlighted the importance of dietary interventions, indicating that high protein supplements can increase muscle synthesis and muscle quality in stroke patients. The role of nutrition in stroke rehabilitation is increasingly recognized, with proteins like branched-chain amino acids showing higher efficacy in skeletal muscle protein synthesis. For the rehabilitation plan of cerebrovascular accident patients, it is crucial to provide nutritional strategies and physical exercises to improve their physical function, cardiopulmonary fitness, muscle power, and overall well-being. When nutritional strategies and training are combined, they can enhance the functional abilities of old-age patients undergoing rehabilitation in their daily routines [28].

EPIDEMIOLOGY

According to Global Burden of Disease (GBD) studies stroke is the second leading cause of death and disability across the world. A large proportion of men are been affected by stroke as compared to women due to some of the risk factors. The global prevalence of stroke, in 2020 was noted as approximately 90 million cases.

Worldwide occurrence of Intracranial haemorrhage (ICH) was approximately 19 million and the worldwide occurrence of subarachnoid haemorrhage (SAH) was approximately 9 million cases. Across 11.71 million people are affected by stroke all over the world. 65% of people across the world are affected by ischemic stroke. About 29% and 6% of people are affected by ICH and SAH respectively. The motility rate of the year 2020 due to stroke was 7.08 million in total out of which 3.48 million were due to ischemia stroke, 3.25 million due to ICH, and 0.35 million by SAH.[30]

Every year approximately 795000 people are affected by new or recurrent stroke, 87% are suffering from ischemia, 10% are suffering from ICH and 3% are suffering from SAH. The number of incidents is increasing or getting worse over the period. Over time from 2010 to 2050, the number of cases of stroke is expected to more than double.[29] Every year, in the US more than 140,000 people are still dying from stroke. Even if the death rate is decreasing over time due to progress in diagnosis, prevention, and treatment. Stroke is one of the fifth leading causes of death in the US.[30] According to the reports published in Economics Times Stroke is the 2nd most leading cause of motility. About 1,85,000 cases of stroke are seen every year in India approximately one stroke case every 40 seconds and one death case due to stroke every 4 minutes.

Stroke carries a high risk of death and disability. Suffer may experience loss of vision or speech, paralysis, and mental impairment. The risk of further episodes of stroke may increase for people having previous episodes of stroke. Blockage of arteries is more dangerous than the rupture of cerebral blood vessels.

According to the survey conducted by the World Health Organization (WHO) annually, 15 million people worldwide suffer from stroke, out of which 5 million die and another 5 million are left permanently disabled. Stroke is uncommon in the age group under 40, it occurs mainly due to high blood pressure. However, stroke also occurs in about 8% of children with sickle cell disease. High blood pressure and tobacco are significant modifiable risks. For every 10 people who die of a stroke, four could be saved if their blood pressure is regulated. Among those aged under 65, two-fifths of deaths from stroke are linked directly to smoking. Arterial fibrillation, heart failure, and heart attacks are other paramount risk factors. The incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure and reduced levels of smoking. However, the absolute number of strokes continues to increase because of the aging population. According to the study of the Global Burden of Disease (GBD), in essence, while the occurrence of stroke has decreased, factors such as the age of those affected, their gender, and their geographical distribution have shifted, leading to a rise in the socio-economic burden associated with stroke over time.[31]

Age-specific stroke: The occurrence of stroke enhances with age and it doubles after the age of 55 years. However, it is more prevalent in the age group between 20 to 54 years

enhancing from 12.9% to 18.6% of all the cases worldwide. The estimated stroke occurrence in China is approximately 331 to 378 cases per 100,000 life years. The second highest stroke incidence rate in Eastern Europe, with an estimated range of 181 to 281 cases per 100,000 life years. Conversely, the lowest stroke incidence is found in Latin America, ranging from 85 to 100 cases per 100,000 life years. [31]

Gender-specific stroke: The incidence of stroke in females and males may depend on age. The occurrence of stroke in females is more common in the younger age group whereas in males, the Old age people are more affected by stroke. Women generally have a higher risk of stroke due to factors related to pregnancy, such as preeclampsia, as well as the use of contraceptives and hormonal therapy. Additionally, conditions like migraine with aura can also contribute to this increased risk in women. Arterial fibrillation enhances the risk of stroke in females over 75 years by 20%, emphasizing the importance of managing this condition in older women.

The National Institutes of Health Stroke Scale categorizes stroke severity, with women having a mean stroke severity of 10 compared to 8.2 for men, indicating potentially more severe strokes in women. Cardioembolic stroke, a severe form of stroke, is more prevalent among women compared to men. Women have a higher fatality rate from stroke, which may be influenced by factors such as delayed acceptance of help for ongoing symptoms. Men commonly experience stroke due to factors like tobacco smoking, excessive alcohol consumption, myocardial infarction, and arterial disorders.[32]

Graphical and racial variations: The global variation in stroke incidence underscores the importance of understanding its multifaceted determinants. One significant study examined a range of factors, including demographics, behavior, physical characteristics, medical history, and laboratory reports, revealing the impact of exposure to air pollution and particulate matter on stroke mortality. [33]

Moreover, a population-based study conducted in northeastern China shed light on the disease landscape in developing countries, providing valuable insights into stroke prevalence and related risks in these regions. Such research is crucial for informing public health policies and interventions tailored to diverse populations worldwide. In many studies, hypertension was found to be a significant factor for stroke, especially for ischemic stroke [34]. The study conducted in the United States identified hypertension as the main cause of stroke and noted geographical variations in the severity of symptoms among stroke sufferers. Additional risk factors highlighted included inadequate physical activity, unhealthy dietary habits, and the consumption of nicotine and alcohol. Disparities in exposure to environmental pollutants like lead and cadmium were also found to affect stroke incidence across different regions. Furthermore, the study observed differences in stroke occurrence between non-Hispanic white and black populations aged 40–50 years [35].

Socio-economic variation: Indeed, a strong inverse relationship exists between stroke incidence and socioeconomic status, primarily due to inadequate access to hospital facilities and post-stroke care among low-income populations. This disparity underscores the importance of addressing healthcare access and equity to reduce the burden of stroke on vulnerable communities [36].

RISK FACTORS [37]

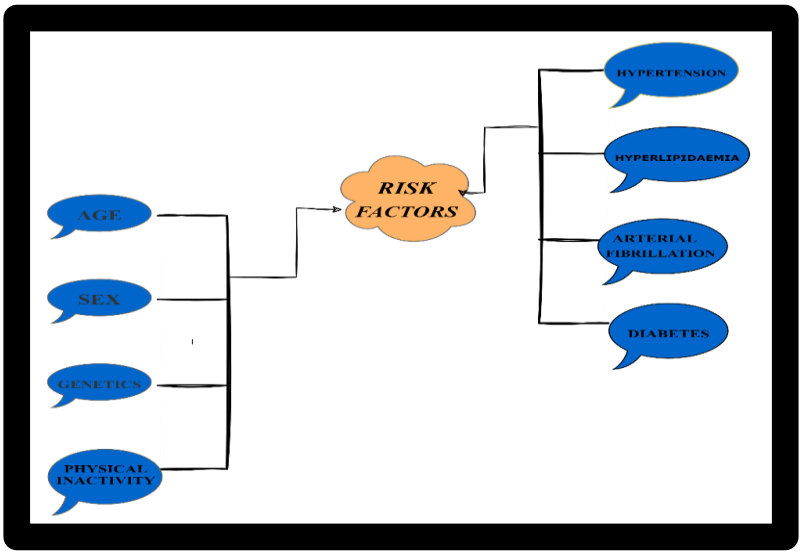

Figure-1 Risk Factors associated with Stroke [37]

The following are some of the risk factors that cause stroke- Age, sex, Genetics, Hypertension, Diabetes, cardia factors, Smoking, Hyperlipidemia, and Alcohol con. Health issues are doubled after the age of 50 years.

1. **Age: -** It is one of the important factors which causes most of the disease. Old age people are more prone to health-related problems. Health issues are doubled after the age of 50 years.
2. **Sex: -** males and females both have a high risk of health problems due to differences in hormones present in them. Males are more prone to stroke due to changes in hormone levels and stress conditions. Females after menopause due to changes in hormone levels are prone to disease. At older ages in mam, the stroke rate is slightly higher than in women.
3. **Race:** African Americans have a higher risk for death and disability from stroke than whites. This is partly because of African- the African-American population has a greater incidence of high blood pressure.
4. **Genetics:** Some of the disease conditions can be transferred from parent genes to genes of young ones. 32 genomes are identified which can be strongly linked to the cause of stroke.
5. **Hypertension:** It is the most significant factor that can cause stroke. A large proportion of patients having hypertension are prone to stroke. Blood pressure 140/90 higher can also damage the arteries supplied to the brain.
6. **Diabetes mellitus:** 20% of people with diabetes are prone to stroke which may lead to death. People with diabetes are at higher risk of stroke than non-diabetics.
7. **Cardiac factors:** cardioembolic infraction in a subtype of ischemia stroke with a high risk of impairment and death. With increase in atrial fibrillation may lead to an

increase in the occurrence of stroke. The atrial fibrillation can be reduced by using an anticoagulant. Heart disease is another significant risk factor for death due to stroke.

8. **Smoking:** This factor doubles the occurrence of stroke.
9. **Hyperlipidemia:** The increase in LDL & VLDL levels can lead to an increase in the occurrence of stroke. The total increase in the cholesterol levels increases the ischemia stroke. Atherosclerosis can enhance the risk of cerebral stroke. High cholesterol levels can contribute to the formation of plaques and hardening of blood vessels. Plaque is a deposition of fatty substances, calcium, and some other substances such as protein, with high lipid content. Accumulation of plaque in the arterial wall decreases the blood flow to the brain through blood vessels. A stroke occurs when the blood supply to arteries is cut off.
10. **Alcohol consumption and substance abuse:** Light to moderate alcohol consumption is highly associated with the occurrence of cerebral stroke where whereas high consumption of alcohol is associated with the cause of cerebral stroke. Some of the drugs such as cocaine, heroin, amphetamines, and cannabis, etc which have high abuse liability are associated with a high risk of cerebral stroke. More than 2 drinks per day may raise blood pressure which can be the leading cause of stroke. Intravenous drug abuse carries a high risk of stroke from cerebral embolism (blood clot).
11. **Obesity and sedentary behavior:** People who are highly physically active are less prone to stroke as compared to physically inactive. The body mass index can also show some effect on the occurrence of stroke due to an increase in body mass the body becomes more prone to disease.
12. **History of TIAs (transient ischemic attacks):** TIAs are often called mini-strokes. They have the same symptoms as stroke but don't last for a longer duration of time. If a person has had one or more TIAs, you are almost 10 times more likely to have a stroke than someone who doesn't have symptoms of stroke or a history of TIAs.
13. **High red blood cell count:** A significant increase in the count of red blood cells leads to thickening of the blood and makes clots more likely. They raise the risk of stroke.
14. **Abnormal heart rhythm:** some types of heart disease may increase the risk of stroke. Having an irregular heart rhythm or heartbeat is the most powerful and treatable heart risk factor for stroke.
15. **Cardiac structure abnormalities:** Damaged heart valves can cause chronic heart damage. Over time, it can increase the risk of stroke.
16. **History of prior stroke:** People are at high risk for having a second stroke after they have already had a stroke.

Other risk factors which may affect the occurrence of stroke

17. **Place where you live:** Stroke is most common among people living in Southeastern County. This may be because of regional differences in lifestyle, race, smoking habits, and diet.
18. **Temperature, season, and climate:** Stroke death occurs more often during extreme temperatures.

19. **Social and economic factors:** There is some evidence that stroke is more common among low-income people.
20. Anxiety, depression, and high-stress levels, as well as working long hours and not having much contact with family, friends, or others outside the home, may raise your risk for stroke.

PATHOPHYSIOLOGY

Assimilating the neurovascular etiology is crucial for resembling the clinical appearance of strokes. The blood supply to the brain is managed by two internal carotid arteries in the fore and vertebral arteries in the posterior. In the pathophysiology of cerebral stroke, when the brain doesn't get a sufficient amount of oxygen due to the narrowing of the blood vessels. Therefore, it leads to a decrease in the blood flow in the cerebral and it affects the different functions of the brain. When the deficiency of blood causes or decreases the uptake of oxygen and glucose to the brain. This process inhibits the metabolism of the cells and due to this it reduces the process of ATP formation and this causes the deficiency of energy production. These changes in the cells of the brain eventually lead to various modifications in the plasma membrane Their function is also affected and it results in necrosis and apoptosis. Necrosis is also called cell death or tissue death which is an irreversible process it leads to various factors such as infection, injury, or lack of blood supply, which leads to the breakage of cells and depletion of cellular structure. On the other side apoptosis which is also known as programmed cell death is the highly regulated process of cell suicide that happens in multicellular organisms. It is a series of biochemical events that guide the controlled dismantling and removal of cells without harm to surrounding tissues. It plays a very decisive role in various physiological actions such as growth, tissue homeostasis, and immune response. These two categories of cell death led to inflammation in the brain and cause cerebral stroke or ischemic stroke.

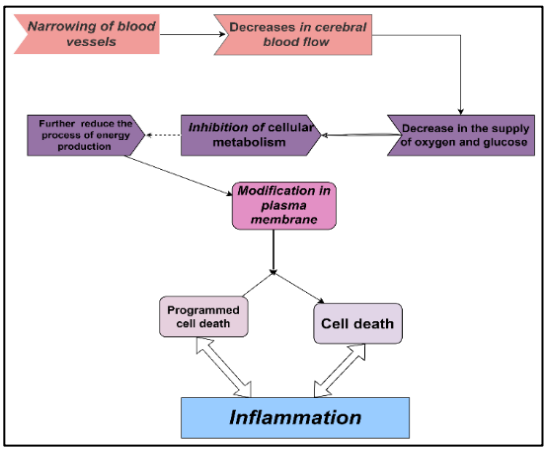

Figure-2 Various stages associated with Stroke

TREATMENT

Stroke can be prevented by modifying risk factors such as hypertension, diabetes, and heart-related diseases within the individuals. Stroke can be managed by managing the

pathophysiology of stroke. Despite extensive research into stroke over the past two decades, there hasn't been a simple way to treat and prevent all the clinical causes of stroke. However, ongoing research is focused on developing novel therapies that target factors involved in both primary and secondary stroke. Various strategies for stroke prevention and treatment are continually being explored and refined to improve outcomes for patients.

1. **Tissue plasminogen activators [TPA]:** It is indeed a naturally occurring protein that plays a crucial role in the breakdown of blood clots by converting plasminogen into plasmin, which then helps dissolve fibrin clots. It is a major endogenous mammalian enzyme with the property of conversion of the inactive proenzyme plasminogen into the active serine protease plasmin. it is found in blood and various organs [38]. While intravenous recombinant tissue plasminogen activator (rt-PA) is often administered in acute ischemic stroke to promote clot fibrinolysis and recanalization, its efficacy in large-vessel occlusion (LVO) strokes is limited. Guidelines often recommend administering rt-PA before mechanical thrombectomy (MT) in LVO strokes due to the potential for earlier recanalization, but it's important to note that successful recanalization by rt-PA alone occurs in only about 10% of cases. This underscores the importance of considering additional interventions like MT for LVO strokes.[39]

Many other effective modes of action are suggested by various experimental observations. rt-PA acts significantly on the ischemic microvasculature as compared to recanalization. The exogenous rt-PA and endogenous t-PA (in patients not receiving rt-PA), cerebral concentration is unknown. By using a sampling and sample preparation protocol involving local microcatheter aspiration from within the occluded vascular field, researchers can measure local cerebral concentrations.

This method appears to offer a novel and efficient way to gather valuable data on the distribution and concentrations of these agents in the affected cerebral tissue, providing insights into their pharmacokinetics and potential effects. It's great to hear that this protocol was published beforehand, indicating a rigorous and transparent research process.[40]

The thrombolytic agent which includes recombinant tissue plasminogen activator(r-TPA) is widely used in the treatment of ischemic stroke. It partially or completely helps in relieving the symptoms of stroke. TPA is a serine protease which is an enzyme that cleaves the peptide bond in proteins. TPA has a corresponding gene in humans i.e. chromosome 8(8P12). It can decompose the fibrin-containing clots. [41] The interleukin - 6(IL-6) is a necessary inflammatory molecule present in stroke.[42] There is a sudden reduction of IL-6 after the administration of r-TPA so its decrease after r-TPA treatment highlights a potential anti-inflammatory effect of the medication. The r-TPA exerts its beneficial effects in acute ischemic stroke and also helps in the dissolution of blood clots.[43] Previous Studies have indeed demonstrated the efficacy of r-TPA in improving neurological impairment in patients with acute ischemic stroke. [44] Administering r-TPA within 3 to 4.5 hours after the onset of symptoms has been shown to lead to better clinical outcomes and performance in these patients. This timeframe is crucial for maximizing the benefits of r-TPA while minimizing the risk of complications, highlighting the importance of prompt recognition and treatment of acute ischemic stroke.[45]

The increasing trend in the use of r-TPA for acute ischemic stroke treatment is seen, as indicated by a study conducted in Australia involving over 100,000 patients. The researchers found a significant rise in the use of r-TPA therapy for stroke. 9.9% in 2006 to 21.8% in 2018, with projections suggesting it may rise to 24% by 2025. This trend likely shows a growing recognition of the benefits of early intervention with r-TPA in acute ischemic stroke and efforts to improve access to timely treatment for eligible patients.[46] Indeed, the use of r-TPA in acute ischemic stroke requires careful consideration of its risks and benefits, particularly regarding the potential for bleeding, which is the most common side effect. Despite recommended guidelines, concerns about bleeding may limit its use in some cases. Therefore, it's crucial to identify patients at risk during the acute phase to prevent neurological deterioration and predict outcomes accurately.
The study conducted in an academic center in the north of Iran aimed to evaluate the outcomes of r-TPA treatment in acute ischemic stroke patients. Additionally, it sought to determine influential factors in predicting favourable or unfavorable outcomes in patients receiving r-TPA. Such research is essential for refining patient selection criteria, optimizing treatment protocols, and improving overall patient care in stroke centers.[47]

2. **Excitotoxicity**: Neuronal death is observed in stroke in large attributes. This phenomenon occurs due to neuronal depolarization and the inability to maintain membrane potential within in the cell. It is mediated by glutamate receptors N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) are first neuroprotective agents tested in preparation for stroke. their untimely release of glutamate can overwhelm the cell's glutamate removal system, leading to excessive calcium influx and protein damage, ultimately not reducing neuronal death in human subjects. Target molecular pathways downstream of excitotoxicity signaling, rather than directly modulating glutamatergic signaling, may reduce side effects and improve stroke outcomes. [48,49]

3.**Gamma amino butyric acid (GABA) agonist:** clomethiazole, barbiturates and benzodiazepine are GABA receptor agonist. Clomethiazole can improve symptoms of stroke in patients but fails to reduce the toxicity that occurs due to glutamate receptors. [50]

4**. Sodium channel blockers**: sodium channel blockers are used as neuroprotective agents and have been used in many animal models for testing. They are used to reduce white matter damage and prevent neuronal death. However, many voltage-gated sodium channel blockers tested in clinical trials have been ineffective. Mexiletine, a sodium channel blocker, has shown effectiveness in treating ischemic stroke in both grey and white matter, but further research is needed to confirm its role. [51] Lubeluzole initially showed a significant reduction in stroke mortality in clinical trials, but subsequent trials did not replicate these results. Similarly, sipatrigine, another sodium and calcium channel blocker, failed to demonstrate efficacy in a Phase II clinical trial for stroke patients. Additionally, amiodarone, while not specifically a sodium channel blocker, was found to worsen brain

injury after stroke by causing defective transportation and accumulation of sodium ions in the brain. [52]

5. **Calcium channel blockers**: Voltage-dependent calcium ion channel blockers have demonstrated potential in decreasing the ischemic damage observed in animal models of brain injury. DP-b99, a calcium ion chelator, has shown a significant effect in Phase I and II clinical trials when administered to stroke patients. In particular, Phase II trials have shown significant improvements in clinical symptoms among stroke patients treated within 12 hours of onset. Some studies suggest that targeting calcium channels could help reduce the occurrence of stroke by 13.5% as compared to diuretics and beta blockers. [53]

6. **Antioxidants**: In the normal brain, the production of reactive oxygen Species (ROS) is balanced by antioxidants generated in the responsive mechanism. However, in cerebral stroke, excess production of free radicals and inactivation of detoxifying agents, disturb the balance, leading to oxidative stress and neuronal injuries. Antioxidants are used in acute stroke treatment to inhibit or scavenge free radicals and degrade them in the system. For instance, AEOL 10,150 effectively regulated gene expression profiles specific to inflammation and stress response, reducing ischemic damage and reperfusion in stroke patients. [54] Deferoxamine regulates hypoxia-inducible factor-1 expression, benefiting from gene activation of factors like vascular endothelial growth factor and erythropoietin, ultimately reducing lesion size and improving sensorimotor capabilities.[55] NXY-059 acts as a scavenger to eliminate free radicals and decrease neurological deficits, as demonstrated in the SAINT clinical trial. However, subsequent trials failed to reproduce its positive effects.[56] Another study involved intravenous injection of antioxidants directly into mouse brains, which reduced neurological defects but had minimal influence on brain damage. These findings highlight the potential of antioxidant therapy in stroke treatment, although further research is needed to clarify its efficacy and optimal administration methods.[57]

Reperfusion: -

The IVT (Intravenous Thrombolytics): - The main purpose of thrombolytic drugs is administered intravenously and they lean on different factors like the clot's duration or age, the thrombolytic agent is like for fibrin, and the presence and duration of neutralizing antibodies [58]. The medications deployed in IVT therapy endeavor to enhance the generation of fibrinolysin, which expedites the disruption of the coagulation barrier of the cerebral vessel. The most effective of IVT medication, recombinant tissue plasminogen activator (rt-PA, or alteplase) arose from examining which is conducted by the US National Institute of Neurological Disorders and Stroke (NINDS)[59]. Therefore, researchers from the European Cooperative Acute Stroke Study (ECASS and ECASS II) were not able to replicate the outcomes accomplished by NINDS. Subsequently, it was detected that this medication effectively reduced the clot diameter in stroke patients within three hours of onslaught. The Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) authorized the effectiveness and safety of alteplase within the specified given time [60]. On the other hand, the class of thrombolytics, comprising both fibrin and non-fibrin agents, is correlated with regulating stroke symptoms. Fibrin

activators serving as alteplase, reteplase, and Tenecteplase directly catalyze the alternation of plasminogen to plasmin, while non-fibrin activators like streptokinase and staphylokinase attain this indirectly [58].

The IAT (Intra-arterial Thrombolytics): - IAT is a different method to access combat acute stroke. The first six hours of onset of MCA occlusion treatment is highly effective, and it's necessary for experienced clinicians and angiographic techniques [53]. The Prolyse in Acute Cerebral Thromboembolism II (PROACT II) and Middle Cerebral Artery Embolism Local Fibrinolytic Intervention (MELT) were arbitrary clinical trials (RCTs) executed to protect a recombinant pro-urokinase medication but generated no actionable data for stroke treatment [61,62]. Thrombolytics and glycoprotein IIb/IIIa antagonists were amalgamated in two minor clinical trials; this approach established the importance of treating atherosclerotic occlusions and their potency was diminished for cardio embolism [63,64]. The Interventional Management of Stroke (IMS) III trial investigated to concurrent use of IVT and IAT to assess the advancement of integrating swift delivery of therapy (IVT) with a highly effective recanalization approach for expedited relief (IAT) [65]. The IMS III trial produced advantageous outcomes with linking therapy (a mixture of IVT and IAT) to evaluate IVT alone. Connecting therapy led to a substantial 69.6% growth in the recanalization extent among stroke patients. [66,67]

Coagulogen depleting agents: -

The latest studies have recognized a robust association between raised fibrinogen levels in stroke patients and unfavourable forecasts for clinical outcomes. Fibrinogen-depleting agents reduced the blood plasma fibrinogen degrees thus thinning blood viscosity and increasing blood circulation. Moreover, they disintegrate arterial blood clumps, thereby reinstating blood flow to the affected cerebral areas. However, while specific Randomized Controlled Trials (RCTs) of fibrinogen therapy exposed the advantageous influence of coagulate-depleting agents in stroke patients, others did not illustrate beneficial effects on clinical outcomes following stroke [68]. Furthermore, specific studies documented the occurrence of bleeding after the Implementation of defibrinogen agents. Ancrod, a defibrinogenating agent originating from snake venom, has been examined for its efficacy in treating ischemic stroke within a three-hour window from onset [69]. As per the record, the European Stroke Treatment with Ancrod Trial (ESTAT) discovered that administering ancrod at a fibrinogen level of 70 mg/dL was both effective and safe, resulting in a decrease in the incidence of intracerebral hemorrhage contrasted to reduced fibrinogen levels.[70]

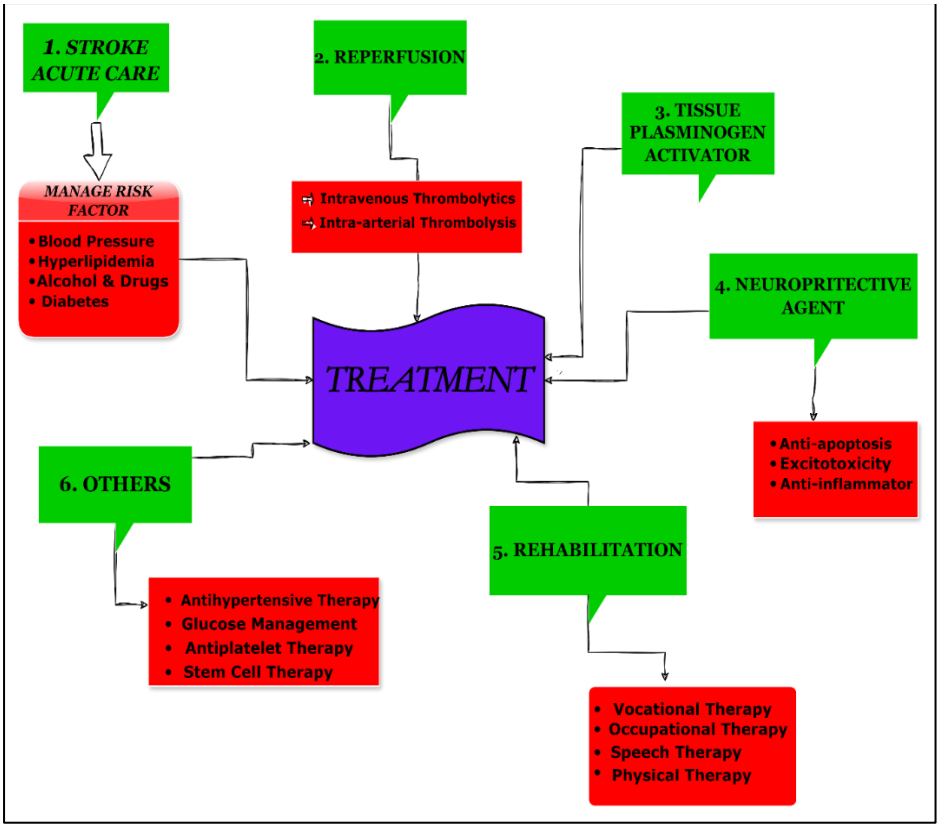

Figure-3 Treatments involved in the management of Stroke

FUTURE PROSPECTIVES

Over the past few years, there has been noticeable progress in the insight into the pathology of cerebrovascular accidents. The discovery of novel drugs has improved drug targeting within the body. Innovative technologies like tele stroke [71] and mobile stroke [72] are now used to decrease illness or death. Hospitals should ensure stroke recovery management after providing primary healthcare. Hospitals should follow standard rules in which timely checkups are done to prevent another stroke episode [73]. Physiotherapists are vital in stroke recovery management. Clinical trials conducted by physiotherapists focus on following rehabilitation processes that include different types of therapies and exercises [74,75]. Substances obtained from natural sources have also proven advantageous in stroke prevention. These substances can be manufactured at a lower cost compared to artificial ones but maintain the same effectiveness and safety. Honokiol is an example of a natural formulation that shows neuroprotective results in preclinical testing and inhibits immune reactions [76]. Future medical trials should not only focus on ascertaining the effect and safety of drugs but also on improving recovery and patient well-being. In particular, medical trials of treatments for stroke rehabilitation must adhere to the following protocol [77]. Patients should ideally be enrolled within two weeks after experiencing stroke symptoms. This should include data sampling or analysis in further studies to ensure typical outcomes. Nowadays, researchers follow understanding guidelines for testing the mechanism of action of drugs and their response to the human body's target parts. In addition to primary care, secondary facilities like recovery improvement or stroke rehabilitation

times should also be documented. This will further demonstrate the effectiveness of therapy. Recent research indicates improvement in stroke treatment by adopting new technology, management, or rehabilitation processes. It is predicted that modern technologies or methods used for stroke treatment will ultimately benefit stroke patients and their well-being.

In recent research, significant progress has been observed in stroke in preclinical trials, based on drug targets and therapeutic strategies. However, despite having these technologies or methods, clinical trials still do not achieve the same results as preclinical trials [78]. Therapies like recanalization show promising outcomes in clinical trials, but only a handful of CVA patients benefit from them [79]. This is why translational preclinical research is still ongoing to improve outcomes in clinical trials. The obstacle in preclinical trials to produce novel drugs is due to patients suffering from stroke along with diseases like high blood pressure and diabetes. Other factors like age, gender, and behavioral outcomes also affect stroke patients [80,81]. Short-term experiments mostly show disappointing results because they often yield negative results during clinical trials [82]. By interpreting the performance and behavioral results, true recovery can be attained, which is still challenging in clinical trials compared to preclinical trials, where animals can smoothly hide these perks [83]. To decrease the translational challenge of stroke, a mixed strategy of recovery and rehabilitation is crucial. Another main problem associated with stroke is data management. In clinical trials, a large amount of data is generated, which should be managed efficiently to be easily assessed by researchers. Industry-academic collaboration plays a crucial role in improving the translational value [84] in stroke research by attaining harmony between industry and academic interests to achieve top-notch results.

Adapting a collaborative approach, leveraging advanced methods, and having defined operational goals are the best processes to overcome translational challenges in stroke research. By focusing on these challenges cumulatively, research can improve preclinical results into more efficient clinical outcomes for stroke patients. [85]

CONCLUSION

Stroke is a second leading cause of motility and impairment in worldwide. This highlights the significant impact of stroke globally and emphasizes the pressing need for more effective therapeutic interventions and improved post-stroke management. While advancements have been made, ischemic stroke remains a serious condition with treatments having both pros and cons. Emerging treatments like tissue plasminogen activator, mechanical thrombolysis and neuroprotectant peptides show promise but require further research. Despite considerable progress in stroke research over the last 25 years, including advancements in experimental models, therapeutic drugs, clinical trials, and rehabilitation studies, substantial knowledge gaps persist in stroke treatment. Improving door-to-needle time and utilizing advanced imaging techniques are crucial. Bridging the gap between preclinical and clinical studies is essential, by following guidelines like Stair and Improve. The route of administration,

especially via the nasal route, holds potential, particularly with nanoparticles. Public awareness is vital to reducing the burden of ischemic stroke. In spite of the heightened occurrence of symptomatic intracerebral haemorrhage, administering intravenous t-PA within three hours of the onset of ischemic stroke led to improved clinical outcomes at three months. This suggests that despite the potential risk of intracerebral haemorrhage associated with t-PA treatment, its benefits in improving clinical outcomes outweigh the risks when administered within the early therapeutic window after ischemic stroke onset. The nasal route indeed bypasses the blood-brain barrier (BBB), making it favourable for delivering medications directly to the brain. Nanoparticles designed for nose-to-brain delivery can be promising for treating cerebral ischemia, as they can potentially enhance drug delivery and efficacy while minimizing systemic side effects. Further more research is needed to ensure reducing motility and disability from stroke globally.

ACKNOWLEDGEMENT

To contend the progress of review article, the authors thank Swami Vivekanand College Pharmacy, Banur for providing efficient resources.

Consent for Publication

Not applicable.

Funding

None

Conflict of Interest

The author declares no conflict of interest, financial or otherwise**.**

REFERENCES

1. Fang, G.; Liu, W.; Wang, L. A machine learning approach to select features important to stroke prognosis. Comput. Biol. Chem., 23 Jun 2020, 88:107316 https://doi.org/10.1016/j.compbiolchem.2020.107316
2. Park, S.J.; Hussain, I.; Hong, S.; Kim, D.; Park, H.; Benjamin, H.C.M. Explainable Artificial Intelligence Model for Stroke Prediction Using EEG Signal. Sensors (Basel). 2022 Dec 15;22(24):9859. doi: 10.3390/s22249859. PMID: 36560227; PMCID: PMC9782764.
3. Tazin, T.; Alam, M.N.; Dola, N.N.; Bari, M.S.; Bourouis, S.; Monirujjaman Khan, M. Stroke Disease Detection and Prediction Using Robust Learning Approaches. J Healthc Eng. 2021 Nov 26; 2021:7633381. doi: 10.1155/2021/7633381.
4. Hui C, Tadi P, Patti L. Ischemic stroke. [Updated 2020 Feb 10]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2020 https://www.ncbi.nlm.nih.gov/books/NBK499997/ Accessed on 25 July 2020.
5. Raichle ME. The pathophysiology of brain ischemia. Ann Neurol. 1983 Jan;13(1):2-10. doi: 10.1002/ana.410130103.

6. Hou K, Xu D, Li F, Chen S, Li Y. The progress of neuronal autophagy in cerebral ischemia stroke: Mechanisms, roles and research methods. J Neurol Sci. 2019 May 15; 400:72-82. doi: 10.1016/j.jns.2019.03.015. Epub 2019 Mar 16.
7. Mukundan G, Seidenwurm DJ. Economic and Societal Aspects of Stroke Management. Neuroimaging Clin N Am. 2018 Nov;28(4):683-689. doi: 10.1016/j.nic.2018.06.009.
8. Paul, S. & Candelario-Jalil, E. Emerging neuroprotective strategies for the treatment of ischemic stroke: An overview of clinical and preclinical studies. Exp. Neurol. 335, 113518 (2021)
9. Krishnamurthi, R. V., Feigin, V. L., Forouzanfar, M. H., Mensah, G. A., Connor, M., Bennett, D. A., et al. (2013). The global and regional burden of first-ever ischaemic and hemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet Glob. Health 1, e259–e281.doi: 10.1016/S2214-109X(13)70089-5
10. Chen S, Zeng L, Hu Z. Progressing hemorrhagic stroke: categories, causes, mechanisms and management. J Neurol. 2014 Nov;261(11):2061-78
11. Ojaghihaghighi S, Vahdati SS, Mikaeilpour A, Ramouz A. Comparison of neurological clinical manifestation in patients with hemorrhagic and ischemic stroke. World J Emerg Med. 2017;8(1):34-38
12. An SJ, Kim TJ, Yoon BW. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. J Stroke. 2017 Jan;19(1):3-10
13. Michael Engh, Costantino I (2010) The science of stroke: mechanisms in search of A treatments. Neuron 67(2): 181–198.
14. Izumi H (2006) Mechanisms of brain injury after global cerebral ischemia.Neurol Clin 24:1–21
15. Wade S (2004) Pathophysiology of focal cerebral ischemia: a therapeutic perspective. J Vasc Interv Radiol 15:S3–S12 (D)
16. Masaharu S (2001) Prediction of tissue survival after middle cerebral artery occlusion based on changes in the apparent diffusion of water. J Neurosurg 95:450–458
17. Sobesky J, Zaro W, Lehnhardt F, Hesselmann V, Thiel A, Dohmen C, Jacobs A, Neveling M, Heiss W (2004) Which time-to-peak threshold best identifies penumbral flow? A comparison of perfusion-weighted magnetic resonance imaging and positron emission tomography in acute ischemic stroke. Stroke35:2843-2847
18. Ashfaq S, Ken B, Askar AM, Maher S, David S (2011) Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. Lancet Neurol 10: 909–921
19. Paul R. (2015) Essential clinical anatomy of the nervous system. In: Paul R Blood Supply of the Brain and Clinical Issues, 1stedn, Academic Press, UK.
20. Aghamiri, S.H.; Assarzadegan, F.; Ghaffari, M.; Khorasani, N.M.; Lima, B.S.; Sepehrirad, A.; Azimi, B.; Delkash, P. Recurrent middle cerebral artery stroke caused by arterial thoracic outlet syndrome and coagulopathy. Radiol. Case Rep. 2022, 17, 1665–1669. [CrossRef] [PubMed]
21. Padilla, C.M.; Foucault, A.; Grimaud, O.; Nowak, E.; Timsit, S. Gender difference of geographic distribution of the stroke incidence affected by socioeconomic, clinical

and urban–rural factors: An ecological study based on data from the Brest stroke registry in France. BMC Public Health 2021, 21, 39. [CrossRef]

22. Pandian, J.; Singh, G.; Kaur, P.; Bansal, R.; Paul, B.; Singla, M.; Singh, S.; Samuel, C.; Litoria, P. Incidence, short-term outcome, and spatial distribution of stroke patients in Ludhiana, India. Neurology 2016, 86, 425–433. [CrossRef]
23. Foley, N.C.; Martin, R.E.; Salter, K.L.; Teasell, R.W. A review of the relationship between dysphagia and malnutrition following stroke. J Rehabil. Med. 2009, 41, 707–713. [CrossRef]
24. Schalk, B.W.M.; Penninx, B.W.J.H.; Bouter, L.M.; Visser, M. Serum albumin and muscle strength: A longitudinal study in older men and women. J. Am. Geriatr. Soc. 2005, 53, 1331–1338. [CrossRef]
25. Okon, M.; Blum, B.; Nathaniel, T.I. Risk factors and ambulatory outcome in ischemic stroke patients with pre-stroke depression. J. Vasc. Nurs. 2021, 39, 91–99. [CrossRef]
26. VanDerwerker, C.J.; Ross, R.E.; Stimpson, K.H.; Embry, A.E.; Aaron, S.E.; Cence, B.; George, M.S.; Gregory, C.M. Combining therapeutic approaches: rTMS and aerobic exercise in post-stroke depression: A case series. Top. Stroke Rehabil. 2018, 25, 61–67. [CrossRef]
27. Yoshimura, Y.; Uchida, K.; Jeong, S.; Yamaga, M. Effects of nutritional supplements on muscle mass and activities of daily living in elderly rehabilitation patients with decreased muscle mass: A randomized controlled trial. J. Nutr. Health Aging 2016, 20, 185–191. [CrossRef]
28. C.W. Tsao, A.W. Aday, Z.I. Almarzooq, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association Circulation, 145 (8) (2022), pp. e153-e639, 10.1161/CIR.0000000000001052
29. E.J. Benjamin, S.S. Virani, C.W. Callaway, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association Circulation, 137 (12) (2018), pp. e67-e492, 10.1161/CIR.0000000000000558
30. Collaborators, G.S. Global, regional, and national burden of stroke, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019, 18, 439–458.
31. Boehme, A.K.; Esenwa, C.; Elkind, M.S. Stroke Risk Factors, Genetics, and Prevention. Circ. Res. 2017, 120, 472–495. [CrossRef]
32. Chen, J.C. Geographic determinants of stroke mortality: Role of ambient air pollution. Stroke 2010, 41,839–841. [CrossRef]
33. Zhang, F.L.; Guo, Z.N.; Wu, Y.H.; Liu, H.Y.; Luo, Y.; Sun, M.S.; Xing, Y.Q.; Yang, Y. Prevalence of stroke and associated risk factors: A population-based cross-sectional study from northeast China. BMJ Open 2017, 7, e015758. [CrossRef] [PubMed]
34. Kiefe, C.I.; Williams, O.D.; Bild, D.E.; Lewis, C.E.; Hilner, J.E.; Oberman, A. Regional disparities in the incidence of elevated blood pressure among young adults: The CARDIA study. Circulation 1997, 96,1082–1088. [CrossRef] [PubMed]
35. Addo, J.; Ayerbe, L.; Mohan, K.M.; Crichton, S.; Sheldenkar, A.; Chen, R.; Wolfe, C.D.; McKevitt, C.Socioeconomic status and stroke: An updated review. Stroke 2012, 43, 1186–1191. [CrossRef]

36. O'Donnell M.J., Chin S.L., Rangarajan S., et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (Interstroke): a case-control study. Lancet. 2016;388:761–775. [PubMed] [Google Scholar]
37. Thiebaut AM, Gauberti M, Ali C, et al. The role of plasminogen activators in stroke treatment: fibrinolysis and beyond. Lancet Neurol. 2018;17(12):1121-1132. doi:10.1016/S1474-4422(18)30323-5PubMedGoogle ScholarCrossref
38. Campbell BC, Mitchell PJ, Churilov L, et al; EXTEND-IA TNK Investigators. Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): a multicenter, randomized, controlled study. Int J Stroke. 2018;13(3):328-334. doi:10.1177/1747493017733935PubMedGoogle ScholarCrossref
39. Kollikowski AM, Schuhmann MK, Nieswandt B, Müllges W, Stoll G, Pham M. Local leukocyte invasion during hyperacute human ischemic stroke. Ann Neurol. 2020;87(3):466-479. doi:10.1002/ana.25665PubMedGoogle ScholarCrossref
40. Jilani TN, Siddiqui AH. Tissue plasminogen activator. Stat-Pearls[Internet]. 2021 [Updated 2021 March 21].
41. Shaafi S, Sharifipour E, Rahmanifar R, Hejazi S, Andalib S, Nikanfar M, et al. Interleukin-6, a reliable prognostic fac- tor for ischemic stroke. Iran J Neurol. 2014; 13(2):70-6. [PMID] [PMCID]
42. Lenglet S, Montecucco F, Denes A, Coutts G, Pinteaux E, Mach F, et al. Recombinant tissue plasminogen activator enhances microglial cell recruitment after stroke in mice. J Cereb Blood Flow Metab. 2014; 34(5):802-12. [DOI:10.1038/ jcbfm.2014.9] [PMID] [PMCID
43. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, Von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: The European Cooperative Acute Stroke Study(ECASS). JAMA. 1995; 274(13):1017-25. [DOI:10.1001/Jama.1995.03530130023023] [PMID]
44. Chen YW, Sung SF, Chen CH, Tang SC, Tsai LK, Lin HJ, et al. Intravenous thrombolysis administration 3-4.5 h after acute ischemic stroke: A retrospective, multicenter study. Front Neurol. 2019; 10:1038. [DOI:10.3389/fneur.2019.01038] [PMID] [PMCID]
45. Marko M, Posekany A, Szabo S, Scharer S, Kiechl S, Kno flach M, et al. Trends of r-tPA (recombinant tissue-type plasminogen activator) treatment and treatment-influencing factors in acute ischemic stroke. Stroke. 2020; 51(4):1240-7. [DOI:10.1161/STROKEAHA.119.027921] [PMID]
46. You S, Saxena A, Wang X, Tan W, Han Q, Cao Y, et al. Efficacy and safety of intravenous recombinant tissue plasminogen activator in mild ischemic stroke: A meta-analysis. Stroke Vasc Neurol.
2018; 3(1):22-7. [DOI:10.1136/svn-2017-000106] [PMID] [PMCID]
47. Hoyte, L.; Barber, P.A.; Buchan, A.M.; Hill, M.D. The rise and fall of NMDA antagonists for ischemic stroke. Curr. Mol. Med. 2004, 4, 131–136. [CrossRef]
48. Wahlgren, N.G.; Bornhov, S.; Sharma, A.; Cederin, B.; Rosolacci, T.; Ashwood, T.; Claesson, L.; CLASS Study Group. The clomethiazole acute stroke study (CLASS):

Efficacy results in 545 patients classified as total anterior circulation syndrome (TACS). J. Stroke Cerebrovasc. Dis. 1999, 8, 231–239. [CrossRef]

49. Carter, A.J. The importance of voltage-dependent sodium channels in cerebral ischemia. Amino Acids 1998, 14, 159–169. [CrossRef]
50. Hewitt, K.E.; Stys, P.K.; Lesiuk, H.J. The use-dependent sodium channel blocker mexiletine is neuroprotective against global ischemic injury. Brain Res. 2001, 898, 281–287. [CrossRef]
51. Kotoda, M.; Hishiyama, S.; Ishiyama, T.; Mitsui, K.; Matsukawa, T. Amiodarone exacerbates brain injuries after hypoxic-ischemic insult in mice. BMC Neurosci. 2019, 20, 62. [CrossRef] [PubMed]
52. Angeli, F.; Verdecchia, P.; Reboldi, G.P.; Gattobigio, R.; Bentivoglio, M.; Staessen, J.A.; Porcellati, C. Calcium channel blockade to prevent stroke in hypertension: A meta-analysis of 13 studies with 103,793 subjects. Am. J. Hypertens. 2004, 17, 817–822. [CrossRef]
53. Bowler, R.P.; Sheng, H.; Enghild, J.J.; Pearlstein, R.D.; Warner, D.S.; Crapo, J.D. A catalytic antioxidant (AEOL10150) attenuates expression of inflammatory genes in stroke. Free Radic. Biol. Med. 2002, 33, 1141–1152. [CrossRef]
54. Ono, S.; Hishikawa, T.; Ogawa, T.; Nishiguchi, M.; Onoda, K.; Tokunaga, K.; Sugiu, K.; Date, I. Effect of deferoxamine-activated hypoxia inducible factor-1 on the brainstem following subarachnoid haemorrhage. In Cerebral Vasospasm; Acta Neurochirurgica Supplement, Volume 104; Springer: Vienna, Austria, 2008; pp. 69–73.
55. Shuaib, A.; Lees, K.R.; Lyden, P.; Grotta, J.; Davalos, A.; Davis, S.M.; Diener, H.C.; Ashwood, T.; Wasiewski, W.W.; Emeribe, U.; et al. NXY-059 for the treatment of acute ischemic stroke. N. Engl. J. Med. 2007, 357, 562–571. [CrossRef]
56. 10. Shirley, R.; Ord, E.N.; Work, L.M. Oxidative Stress and the Use of Antioxidants in Stroke. Antioxidants 2014, 3, 472–501. [CrossRef]
57. Barreto, A.D. Intravenous thrombolytics for ischemic stroke. Neurotherapeutics 2011, 8, 388–399. [CrossRef]
58. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N. Engl. J. Med. 1995, 333, 1581–1587. [CrossRef] [PubMed]
59. Külkens, S.; Hacke, W. Thrombolysis with alteplase for acute ischemic stroke: Review of SITS-MOST and other Phase IV studies. Expert Rev. Neurother. 2007, 7, 783–788. [CrossRef] [PubMed]
60. Furlan, A.; Higashida, R.; Wechsler, L.; Gent, M.; Rowley, H.; Kase, C.; Pessin, M.; Ahuja, A.; Callahan, F.; Clark, W.M.; et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: A randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 1999, 282, 2003–2011. [CrossRef] [PubMed]
61. Ogawa, A.; Mori, E.; Minematsu, K.; Taki, W.; Takahashi, A.; Nemoto, S.; Miyamoto, S.; Sasaki, M.; Inoue, T.; The MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery

stroke: The middle cerebral artery embolism local fibrinolytic intervention trial(MELT) Japan. Stroke 2007, 38, 2633–2639. [CrossRef]

62. Abou-Chebl, A.; Bajzer, C.T.; Krieger, D.W.; Furlan, A.J.; Yadav, J.S. Multimodal therapy for the treatment of severe ischemic stroke combining GPIIb/IIIa antagonists and angioplasty after failure of thrombolysis. Stroke 2005, 36, 2286–2288. [CrossRef]
63. Qureshi, A.I.; Harris-Lane, P.; Kirmani, J.F.; Janjua, N.; Divani, A.A.; Mohammad, Y.M.; Suarez, J.I.; Montgomery, M.O. Intra-arterial reteplase and intravenous abciximab in patients with acute ischemic stroke: An open-label, dose-ranging, phase I study. Neurosurgery 2006, 59, 789–796; discussion 796–787. [CrossRef]
64. Investigators, I.I.T. The Interventional Management of Stroke (IMS) II Study. Stroke 2007, 38, 2127–2135. [CrossRef]
65. Mazighi, M.; Meseguer, E.; Labreuche, J.; Amarenco, P. Bridging therapy in acute ischemic stroke: A systematic review and meta-analysis. Stroke 2012, 43, 1302–1308. [CrossRef]
66. Jung, S.; Stapf, C.; Arnold, M. Stroke unit management and revascularisation in acute ischemic stroke. Eur. Neurol. 2015, 73, 98–105. [CrossRef]
67. Chen, J.; Sun, D.; Liu, M.; Zhang, S.; Ren, C. Defibrinogen Therapy for Acute Ischemic Stroke: 1332 Consecutive Cases. Sci. Rep. 2018, 8, 9489. [CrossRef]
68. Hao, Z.; Liu, M.; Counsell, C.; Wardlaw, J.M.; Lin, S.; Zhao, X. Fibrinogen depleting agents for acute ischaemic stroke. Cochrane Database Syst. Rev. 2012. [CrossRef] [PubMed]0
69. Levy, D.E.; Trammel, J.; Wasiewski, W.W.; For the Ancrod Stroke Program (ASP) Study Team. Ancrod for acute ischemic stroke: A new dosing regimen derived from analysis of prior ancrod stroke studies. J. Stroke Cerebrovasc. Dis. 2009, 18, 23–27. [CrossRef] [PubMed]
70. Akbik, F.; Hirsch, J.A.; Chandra, R.V.; Frei, D.; Patel, A.B.; Rabinov, J.D.; Rost, N.; Schwamm, L.H.; Leslie-Mazwi, T.M. Telestroke-the promise and the challenge. Part one: Growth and current practice. J. Neurointerv. Surg. 2017, 9, 357–360. [CrossRef]
71. Bowry, R.; Parker, S.; Rajan, S.S.; Yamal, J.M.; Wu, T.C.; Richardson, L.; Noser, E.; Persse, D.; Jackson, K.; Grotta, J.C. Benefits of Stroke Treatment Using a Mobile Stroke Unit Compared With Standard Management: The BEST-MSU Study Run-In Phase. Stroke 2015, 46, 3370–3374. [CrossRef]
72. Association, A.H. New Recommendations for Stroke Systems of Care to Improve Patient Outcomes; ScienceDaily: Rockville, MD, USA, 2019.
73. Arienti, C.; Lazzarini, S.G.; Pollock, A.; Negrini, S. Rehabilitation interventions for improving balance following stroke: An overview of systematic reviews. PLoS ONE 2019, 14, e0219781. [CrossRef]
74. Bonini-Rocha, A.C.; de Andrade, A.L.S.; Moraes, A.M.; Gomide Matheus, L.B.; Diniz, L.R.; Martins, W.R. Effectiveness of Circuit-Based Exercises on Gait Speed, Balance, and Functional Mobility in People Affected by Stroke: A Meta-Analysis. PM R 2018, 10, 398–409. [CrossRef]
75. Zhang, P.; Liu, X.; Zhu, Y.; Chen, S.; Zhou, D.; Wang, Y. Honokiol inhibits the inflammatory reaction during cerebral ischemia-reperfusion by suppressing NF-κB

activation and cytokine production of glial cells. Neurosci. Lett. 2013, 534, 123–127. [CrossRef]

76. Chollet, F.; Cramer, S.C.; Stinear, C.; Kappelle, L.J.; Baron, J.C.; Weiller, C.; Azouvi, P.; Hommel, M.; Sabatini, U.; Moulin, T.; et al. Pharmacological therapies in post stroke recovery: Recommendations for future clinical trials. J. Neurol. 2014, 261, 1461–1468. [CrossRef]
77. Khandelwal, P.; Yavagal, D.R.; Sacco, R.L. Acute Ischemic Stroke Intervention. J. Am. Coll. Cardiol. 2016, 67, 2631–2644. [CrossRef]
78. Boltze, J.; Ayata, C. Challenges and Controversies in Translational Stroke Research—An Introduction. Transl. Stroke Res. 2016, 7, 355–357. [CrossRef] [PubMed]
79. Endres, M.; Engelhardt, B.; Koistinaho, J.; Lindvall, O.; Meairs, S.; Mohr, J.P.; Planas, A.; Rothwell, N.; Schwaninger, M.; Schwab, M.E.; et al. Improving outcome after stroke: Overcoming the translational roadblock. Cerebrovasc. Dis. 2008, 25, 268–278. [CrossRef] [PubMed]
80. Zerna, C.; Hill, M.D.; Boltze, J. Towards Improved Translational Stroke Research: Progress and Perspectives of the Recent National Institute of Neurological Disorders and Stroke Consensus Group Meeting. Stroke2017, 48, 2341–2342. [CrossRef] [PubMed]
81. Fisher, M.; Feuerstein, G.; Howells, D.W.; Hurn, P.D.; Kent, T.A.; Savitz, S.I.; Lo, E.H.; Group, S. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke 2009, 40, 2244–2250. [CrossRef]
82. Boltze, J.; Lukomska, B.; Jolkkonen, J.; For the MEMS–IRBI Consortium. Mesenchymal stromal cells in stroke: Improvement of motor recovery or functional compensation? J. Cereb. Blood Flow Metab. 2014, 34, 1420–1421. [CrossRef]
83. Boltze, J.; Wagner, D.C.; Barthel, H.; Gounis, M.J. Academic-industry Collaborations in Translational Stroke Research. Transl. Stroke Res. 2016, 7, 343–353. [CrossRef]
84. Wang, L.; Plump, A.; Ringel, M. Racing to define pharmaceutical R&D external innovation models. Drug Discov. Today 2015, 20, 361–370

.