A Study of Stroke Disease: Current Treatment and Analysing with Strategies

Bhagyashri Jitendra Salunke[1*], Syeda Afifa[2]

[1]Student, Department of Pharmacy
[2]Assistant Professor, Department of Pharmacy
[1,2]Sayali Charitable Trust's College of Pharmacy, Chhatrapati Sambhajinagar, Maharashtra, India

Abstract:
Stroke is a clinically defined syndrome of acute, focal neurological deficit attributed to vascular injury (infarction, haemorrhage) of the central nervous system. Stroke is the second leading cause of death and disability worldwide. Stroke is not a single disease but can be caused by a wide range of risk factors, disease processes and mechanisms. Hypertension is the most important modifiable risk factor for stroke, although its contribution differs for different subtypes. Most (85%) strokes are ischaemic, predominantly caused by small vessel arteriolosclerosis, cardioembolism and large artery athero-thromboembolism. Ischaemic strokes in younger patients can result from a different spectrum of causes such as extracranial dissection. Approximately 15% of strokes worldwide are the result of intracerebral haemorrhage, which can be deep (basal ganglia, brainstem), cerebellar or lobar. Deep haemorrhages usually result from deep perforator (hypertensive) arteriopathy (arteriolosclerosis), while lobar haemorrhages are mainly caused by cerebral amyloid angiopathy or arteriolosclerosis. A minority (about 20%) of intracerebral haemorrhages are caused by macrovascular lesions (vascular malformations, aneurysms, cavernomas), venous sinus thrombosis or rarer causes; these are particularly important in young patients (<50 years). Knowledge of vascular and cerebral anatomy is important in localizing strokes and understanding their mechanisms. This guides rational acute management, investigation, and secondary prevention.

Keywords: Cerebrovascular disease; MRCP; intracerebral haemorrhage; ischaemic stroke; stroke pathogenesis; stroke risk factors; transient ischaemic attack.[1]

1.1 Introducation: Acute stroke is frequently referred to as a cerebrovascular accident; however, it is essential to note that a stroke is not an accidental event. A more accurate and meaningful term to describe it is "brain attack," which carries a similar significance to "heart attack." However, stroke encompasses a broader range of variations than heart disease. Stroke is categorized into mainly 2 types: ischemic and hemorrhagic. Hemorrhagic strokes are further divided into intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), more specifically, nontraumatic (spontaneous) ICH and nontraumatic (spontaneous aneurysmal) SAH.

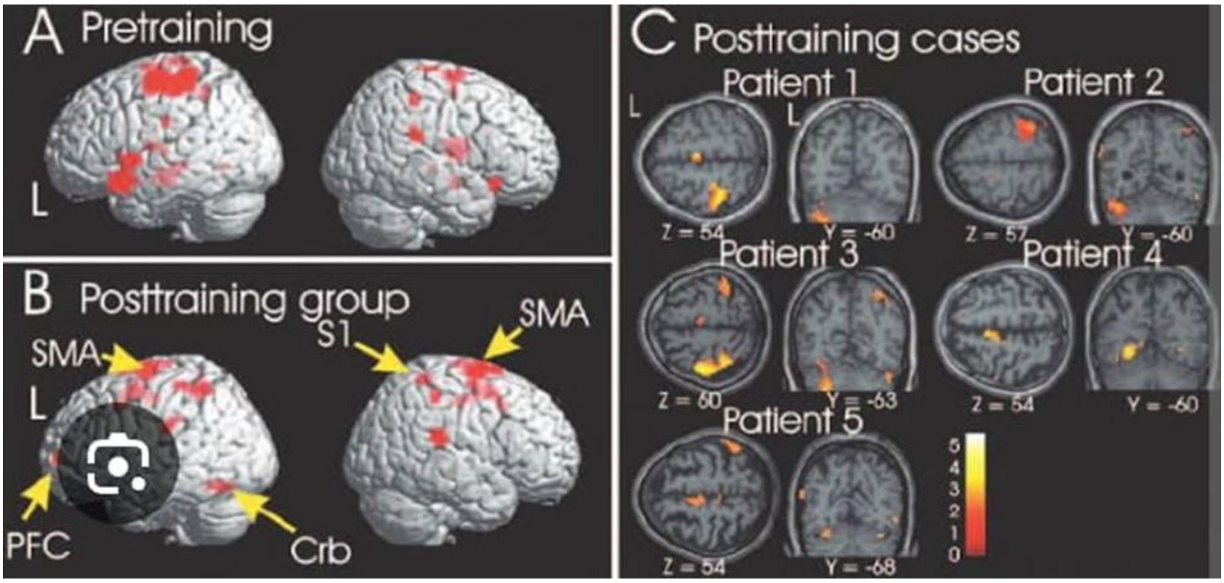
Ischemic strokes occur when there is a blockage in a blood vessel, resulting in a restricted blood supply to the brain. In contrast, hemorrhagic strokes occur when a blood vessel ruptures, causing blood to leak into the intracranial cavity.

International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

The American Heart Association/The American Stroke Association (AHA/ASA) provides a comprehensive definition of stroke. In its simplest form, stroke is an acute episode of focal neurological dysfunction that persists for more than 24 hours.

Stroke ranks as the second leading cause of death worldwide and is a major contributor to disability.[Stroke imposes a considerable financial burden due to the costs associated with prehospital, hospital, and posthospital care.

Understanding that the potential for achieving a complete neurological recovery diminishes with every minute of untreated acute stroke is essential. This forms the "time is brain" concept foundation, emphasizing the critical importance of timely evaluation and management of an acute stroke. Early and targeted treatments, rehabilitation programs, and long-term lifestyle modifications can significantly enhance clinical outcomes for individuals with an acute stroke. This can hopefully lead to maximal clinical recovery in each patient and decrease the global impact of stroke.[2]



1.2 Types of stroke: ischemic stroke occurs when a blood vessel that supplies the brain becomes blocked or "clogged" and impairs blood flow to part of the brain. The brain cells and tissues begin to die within minutes from lack of oxygen and nutrients. Ischemic strokes are further divided into 2 groups:

1.2.1 Thrombotic strokes. These are caused by a blood clot that develops in the blood vessels inside the brain.

1.2.2 Embolic strokes. These are caused by a blood clot or plaque debris that develops elsewhere in the body and then travels to one of the blood vessels in the brain through the bloodstream

1.3 Thrombotic stroke

Thrombotic strokes are strokes caused by a thrombus (blood clot) that develops in the arteries supplying blood to the brain. This type of stroke is usually seen in older persons, especially those with high cholesterol and atherosclerosis (a buildup of fat and lipids inside the walls of blood vessels) or diabetes.

Sometimes, symptoms of a thrombotic stroke can occur suddenly and often during sleep or in the early morning. At other times, it may occur gradually over a period of hours or even days.

Thrombotic strokes may be preceded by one or more "mini-strokes," called transient ischemic attacks, or TIAs. TIAs may last for a few minutes or up to 24 hours, and are often a warning sign that a stroke may occur. Although usually mild and transient, the symptoms caused by a TIA are similar to those caused by a stroke.

Another type of stroke that occurs in the small blood vessels in the brain is called a lacunar infarct. The word lacunar comes from the Latin word meaning "hole" or "cavity." Lacunar infarctions are often found in people who have diabetes or high blood pressure

1.4 Embolic stroke

Embolic strokes are usually caused by a blood clot that forms elsewhere in the body (embolus) and travels through the bloodstream to the brain. Embolic strokes often result from heart disease or heart surgery and occur rapidly and without any warning signs. About 15% of embolic strokes occur in people with atrial fibrillation, a type of abnormal heart rhythm in which the upper chambers of the heart do not beat effectively.

1.5 Hemorrhagic stroke:

Hemorrhagic strokes occur when a blood vessel that supplies the brain ruptures and bleeds. When an artery bleeds into the brain, brain cells and tissues do not get oxygen and nutrients. In addition, pressure builds up in surrounding tissues and irritation and swelling occur, which can lead to further brain damage. Hemorrhagic strokes are divided into 2 main categories, including the following:

1.5.1 Intracerebral hemorrhage. Bleeding is from the blood vessels within the brain.
1.5.2 Subarachnoid hemorrhage. Bleeding is in the subarachnoid space (the space between the brain and the membranes that cover the brain).

1.6 Intracerebral hemorrhage:

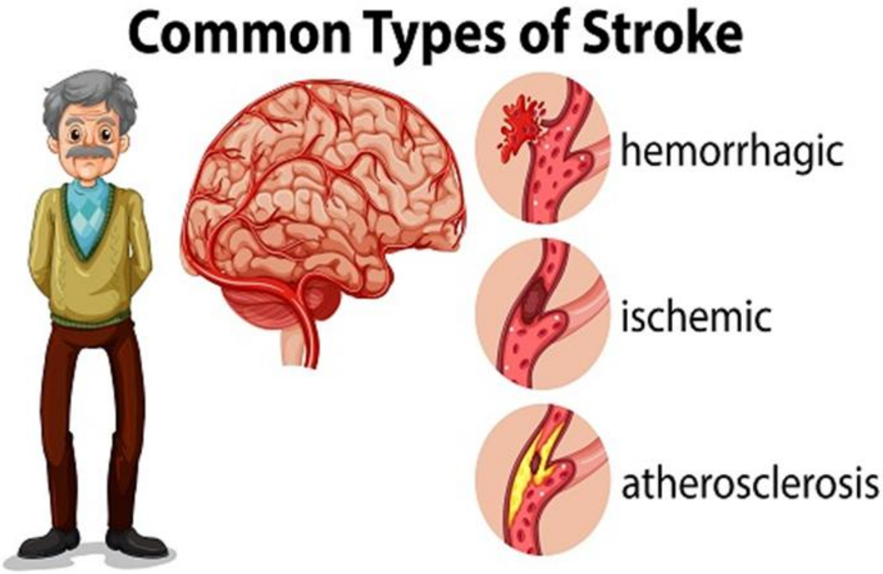
Intracerebral hemorrhage is usually caused by high blood pressure. Bleeding occurs suddenly and rapidly. There are usually no warning signs and bleeding can be severe enough to cause coma or death.

1.7 Subarachnoid hemorrhage

Subarachnoid hemorrhage results when bleeding occurs between the brain and the membrane that covers the brain (meninges) in the subarachnoid space. This type of hemorrhage is often due to an aneurysm or an arteriovenous malformation (AVM). It can also be caused by trauma.

1.7.1 An aneurysm is a weakened, ballooned area on an artery wall and has a risk for rupturing. Aneurysms may be congenital (present at birth), or may develop later in life due to such factors as high blood pressure or atherosclerosis.

1.7.2 An AVM is a congenital disorder that consists of a disorderly tangled web of arteries and veins. The cause of AVM is unknown, but it is sometimes genetic or part of certain syndromes.[3]



1.8 Complication of stroke:

The complications of acute ischemic stroke are many and common.These include, but are not limited to:

- Deep vein thrombosis and pulmonary embolism: DVT prophylaxis is recommended.
- Aspiration and pneumonia: A swallowing evaluation before feeding is always indicated and is a requirement for stroke center accreditation.
- Seizures
- Depression
- Cerebral edema and increased ICP[5]

1.9 Treatment of stroke: acute reperfusion theraphy

1.9.1 Intravenous alteplase (within 4.5 hours of stroke onset)

The American Heart Association (AHA) and American Stroke Association (ASA) recommend IV alteplase (tPA) for patients who meet the inclusion criteria and have symptom onset or last known well time within 3 hours.[IV tPA should be administered at a dose of 0.9 mg/kg, with a maximum dose of 90 mg. The first 10% of the dose is given as an initial bolus over 1 minute, followed by the remaining 90% infused over 60 minutes. The treatment window has been extended to 4.5 hours for selected candidates.

Inclusion criteria include a diagnosis of ischemic stroke with a measurable neurological deficit, symptom onset within 3 hours before treatment, and age 18 years or older.

Healthcare providers must review the exclusion criteria for thrombolytic agents before administering tPA. According to the FDA, contraindications to IV thrombolysis include active internal bleeding, recent intracranial surgery or severe head trauma, intracranial conditions that increase bleeding risk, bleeding diathesis, severe uncontrolled hypertension, current intracranial hemorrhage, subarachnoid hemorrhage, and a recent history of stroke.

Healthcare providers must weigh the benefits and risks of treatment for patients presenting between 3 and 4.5 hours after symptom onset. Additional relative exclusion criteria in this time window include patients aged 80 or older, an NIHSS score greater than 25, use of oral anticoagulants, and a history of both diabetes and prior ischemic stroke.[6]

1.9.2 Magnetic resonance imaging–guided thrombolysis for stroke with unknown time of onset

Many patients wake up with symptoms of an acute stroke, rendering them ineligible for IV thrombolytic therapy because their last known normal state was at bedtime. The WAKE-UP Stroke Trial utilized the mismatch between a positive DWI MRI sequence, indicating an acute ischemic infarction, and a negative FLAIR MRI sequence, which suggests that the infarct occurred within 4.5 hours of the MRI. DWI becomes positive within 30 minutes of an acute infarct, while the FLAIR sequence typically remains negative until about 4.5 hours after onset. This mismatch indicates the stroke occurred within the 4.5-hour window, making the patient eligible for IV thrombolytic therapy. The WAKE-UP Stroke Trial confirmed the positive result.[7]

1.9.3 Intravenous tenecteplase (within 4.5 hours of stroke onset)

Tenecteplase (TNK), another fibrinolytic agent, may be considered an alternative to alteplase. TNK offers advantages over alteplase, including a longer half-life and the ability to be administered as a single IV bolus. TNK is typically given as a weight-based IV bolus of 30 to 50 mg over 5 seconds. TNK has increasingly become the fibrinolytic agent of choice at many stroke centers, particularly during the COVID-19 pandemic.

Recent studies indicate that TNK has a comparable efficacy and safety profile to tPA. According to the 2023 AHA guidelines, it may be reasonable to choose TNK over alteplase in patients who have no contraindications to IV fibrinolytics and are also eligible for mechanical thrombectomy. Notably, a dose of 0.4 mg/kg has not demonstrated any advantage over the 0.25 mg/kg dose.[8]

Mechanical thrombectomy should be considered for all eligible patients, including those who have received fibrinolytic **Mechanical thrombectomy (within 6 hours of stroke onset)**

therapy. The AHA/ASA guidelines recommend proceeding with mechanical thrombectomy without waiting to observe the response to IV tPA in patients who qualify for the procedure.

In recent years, acute stroke care has seen significant advancements. Multiple trials conducted in 2015 demonstrated that endovascular thrombectomy within the first 6 hours significantly outperforms standard medical care in patients with large vessel occlusion (LVO) affecting the proximal anterior circulation. These benefits are consistent across various geographic regions and patient populations. Please see StatPearls' companion resource, "Acute Stroke," for more information.[9]

1.9.4 Mechanical thrombectomy with perfusion study (within 16 to 24 hours of stroke onset)

Perfusion imaging studies (eg, CT perfusion or MR perfusion) can define the areas of the brain that are ischemic but not yet infarcted, known as the ischemic penumbra. Depending on the size of the penumbra relative to the ischemic core, a significant amount of brain tissue can be saved by restoring blood flow in cases of LVO identified on CT or MR angiography, leading to improved clinical outcomes.

In 2018, a significant paradigm shift occurred in stroke care. The DAWN trial showed significant benefits of endovascular thrombectomy in patients with LVO in the arteries of the proximal anterior circulation. This trial extended the stroke window to 24 hours in selected patients using perfusion imaging. Subsequently, more patients can be treated, even up to 24 hours.

Mechanical thrombectomy is recommended within 6 to 16 hours of the last known normal in selected patients with LVO acute ischemic stroke in the anterior circulation who meet the DAWN and DEFUSE 3 criteria. For selected patients meeting DAWN criteria, mechanical thrombectomy may be considered reasonable up to 24 hours after the last known normal.[10]

1.9.5 Acute Hospital Management

1.9.5 [1]Blood pressure:

Guidelines recommend maintaining BP below 180/105 mmHg for the first 24 hours following IV tPA administration.[34] The 2023 AHA guidelines recommend maintaining BP at or below 185/110 mmHg before the procedure in patients scheduled for mechanical thrombectomy who have not received IV fibrinolytic therapy. Additionally, a new recommendation advises an initial 15% reduction in blood pressure for patients with comorbidities such as acute heart failure or aortic dissection.[11]

1.9.5 [2] Temperature:

Hyperthermia (>38 °C) should be avoided and managed appropriately using antipyretics such as acetaminophen. Common sources of infection, including pneumonia and urinary tract infections, should be identified and treated. Currently, there is insufficient evidence to support the routine use of therapeutic hypothermia in acute ischemic stroke[12]

1.9.5 [3] Antiplatelet treatment:

Aspirin is recommended within 24 to 48 hours of symptom onset in patients with ischemic stroke. A Cochrane review found that initiating aspirin within 48 hours reduces the risk of recurrent ischemic stroke and improves long-term outcomes, without a significant increase in early intracranial hemorrhage risk.[13]

1.9.6 [4] Statins:

High-intensity statins (atorvastatin 80 mg daily or rosuvastatin 20 mg daily) are recommended for patients under 75 years old with clinical atherosclerotic cardiovascular disease. Patients already taking statins before their ischemic stroke may continue their therapy.[14]

1.10 Symptoms of stroke:

The signs and symptoms of a stroke often occur quickly. However, they can develop over hours or even days. This sometimes happens when a transient ischemic attack (TIA) — a blockage that breaks up before it damages your brain — turns into a stroke. Sudden confusion, trouble speaking, or trouble understanding speech

1 Sudden numbness or weakness, especially on one side of the body
2. Sudden severe headache with no known cause

3. Sudden trouble seeing from one or both eyes
4. Sudden trouble walking, dizziness, or loss of balance or coordination

The FAST test can help you remember what to do if you think someone is having a stroke.

- **F — Face:** Ask the person to smile. Does one side of the face droop?
- **A — Arms:** Ask the person to raise both arms. Does one arm drift downward?
- **S — Speech:** Ask the person to repeat a simple phrase. Is their speech slurred or strange?
- **T — Time:** If you observe any of these signs, Early treatment is essential.

If you think you or someone else may be having a TIA or stroke, do not drive to the hospital or let someone else drive you. Call an ambulance so that medical personnel can begin lifesaving treatment on the way to the emergency room. During a stroke, **every minute counts.[28]**

1.11 Risk factor of stroke:

1.11. [1] High blood pressure:

High blood pressure is a leading cause of stroke. It occurs when the pressure of the blood in your arteries is too high.

1.11.[2] High cholesterol:

Cholesterol is a waxy, fat-like substance made by the liver and found in certain foods. Your liver makes enough for your body's needs, but we often get more cholesterol from the foods we eat. If we take in more cholesterol than the body can use, the extra cholesterol can build up in the arteries, including those of the brain. This can lead to narrowing of the arteries, stroke, and other problems

1.11. [3] Heart disease:

Common heart disorders can increase your risk for stroke. For example, coronary artery disease increases your risk for stroke, because plaque builds up in the arteries and blocks the flow of oxygen-rich blood to the brain.

1.11.[4] Diabetes:

Diabetes increases your risk for stroke. Diabetes causes sugars to build up in the blood and prevent oxygen and nutrients from getting to the various parts of your body, including your brain. High blood pressure is also common in people with diabetes. High blood pressure is the leading cause of stroke and is the main cause for increased risk of stroke among people with diabetes.

1.11. [5] Sickle cell disease:

Sickle cell disease is a blood disorder linked to ischemic stroke that affects mainly Black children. The disease causes some red blood cells to form an abnormal sickle shape. A stroke can happen if sickle cells get stuck in a blood vessel and block the flow of blood to the brain.

1.11. [6] Other factor that affecting on stroke:

1.11. [7] Family history:

Family members share genes, behaviors, lifestyles, and environments that can influence their health and their risk for disease. Stroke risk can be higher in some families than in others. Your chances of having a stroke can go up or down depending on your age, sex, and race or ethnicity.

1.11 [8] Genetics and family history:

When members of a family pass traits from one generation to another through genes, that process is called heredity.

Genetic factors likely play some role in high blood pressure, stroke, and other related conditions. Several genetic disorders can cause a stroke, including sickle cell disease. People with a family history of stroke are also likely to share common environments and other potential factors that increase their risk.

1.11. [9] Age:

The older you are, the more likely you are to have a stroke. The chance of having a stroke about doubles every 10 years after age 55. Although stroke is common among older adults, many people younger than 65 years also have strokes

1.11. [10] Sex:

Stroke is more common in women than in men, and women of all ages are more likely than men are to die from stroke.4 Pregnancy and use of birth control pills pose special stroke risks for women[15]

1.12 Pharmacological treatment of stroke:

Pharmacologic therapy for stroke may be divided into stroke-specific treatment and stroke prevention.[9] The pharmacologic treatment of a stroke depends upon whether the stroke is ischemic or hemorrhagic. Pharmacotherapeutic options for primary ischemic stroke are tissue plasminogen activator (tPA) and—under defined conditions—antiplatelet agents. Pharmacotherapeutic treatment for hemorrhagic stroke is aimed at controlling the patient's blood pressure and intracranial pressure**.**

1.12.[1] Treatment of Ischemic Stroke:

tPA: Of the available IV tPA agents, alteplase is the only one that is FDA approved to treat ischemic stroke. This indication was granted after the drug's efficacy was demonstrated in the NINDS rt-PA Stroke Study. This study, which included 624 patients randomized to receive 0.9 mg/kg (maximum 90 mg) of IV tPA or placebo, found that those receiving tPA (£3 hours of symptom onset) were at least 30% more likely than those receiving placebo to have minimal or no disability 3 months after treatment

Antiplatelet Agents: Aspirin is the only oral antiplatelet agent that has been evaluated for the treatment of acute ischemic stroke. Aspirin therapy (325 mg) should begin within 24 to 48 hours of an ischemic stroke, but not within 24 hours of completion of alteplase therapy.Alternatively, it is recommended that patients who are ineligible for treatment with a thrombolytic agent receive early aspirin therapy (starting dose 150-325 mg). Although there is an increased risk of bleeding with aspirin use, a beneficial role is seen when aspirin is administered during acute ischemic stroke.[16]

1.12.[2] Treatment of Hemorrhagic Stroke:

Treatment Options: While hemorrhagic stroke accounts for about 15% of stroke occurrences per year, the death rate for these patients is disproportionately high (50%).[2] Pharmacologic treatment options for hemorrhagic stroke are limited. Treatment of any patient who has experienced a hemorrhagic stroke includes the following steps: determining the cause of bleeding; controlling the patient's blood pressure; stopping any medications that may heighten the risk of further bleeding; and controlling the patient's intracranial pressure[17] ll medications that increase the risk of bleeding, such as warfarin, aspirin, and heparin, should be discontinued in a patient having a hemorrhagic stroke. If the intracranial hemorrhage is caused specifically by warfarin, the patient's international normalized ratio (INR) may be corrected through the administration of IV vitamin K and fresh-frozen plasma.[17] The administration of 10 mg of IV vitamin K will potentially normalize the INR in 6 to 24 hours; additional doses of 5 to 10 mg every 12 hours may be given, to a maximum dose of 25 mg.[17]

Fig: Clopidogrel &Aspirin Tablet[18]

1.13 Clopidogrel Mechanisum of Action : Clopidogrel is an irreversible inhibitor of the platelet P2Y12 adenosine diphosphate receptor. Inhibition of this receptor prevents the downstream activation of the glycoprotein IIb/IIIa receptor complex, which leads to reduced platelet aggregation. Clopidogrel is an inactive prodrug that requires enzymatic activation via various CYP enzymes, including the CYP2C19 and CYP3A4 enzymes, through a 2-step bioactivation process. Genetic polymorphisms of these enzymes can influence the response to therapy. The most commonly discussed genetic polymorphism related to clopidogrel is that of one or both alleles of the CYP2C19 enzyme. Patients with any loss of function allele will not effectively metabolize clopidogrel, leading to the inability to inhibit platelet activity. For example, patients who are homozygous for these non-functioning alleles often demonstrate the poorest metabolism and subsequent activation of clopidogrel, as indicated by high on-treatment platelet reactivity during platelet function testing.

In a normal metabolizer, the drug typically has a bioavailability of 50%, with only 15% of an oral dose becoming active via esterase hydrolysis with the CYP enzymes[19]

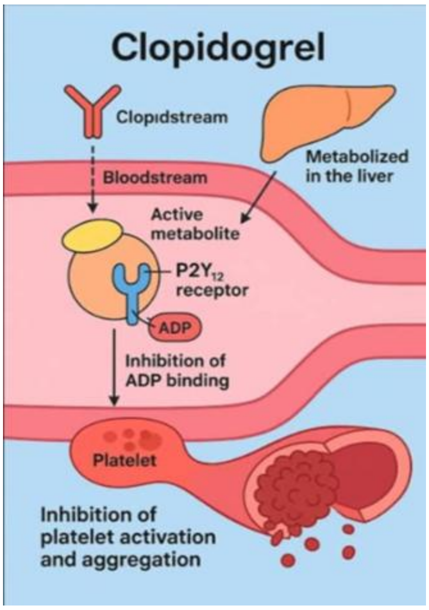


Fig: Clopidogrel MOA[20]

International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

1.14 Aspirin Of Mechanism of Action : Aspirin is a cyclooxygenase-1 (COX-1) inhibitor. It is a modifier of the enzymatic activity of cyclooxygenase-2 (COX-2).Unlike other NSAIDs (ibuprofen/naproxen), which bind reversibly to this enzyme, aspirin binding is irreversible.[5] It also blocks thromboxane A2 on platelets in an irreversible fashion preventing platelet aggregation

Researchers hypothesize that due to the blocking of the COX pathway, the arachidonic acids are shuttled into the lipoxygenase pathway. The production of anti-inflammatory lipoxins results from modifying prostaglandin-endoperoxide synthase (PTGS2), also called COX-2, that results in the production of lipoxins, most of which are anti-inflammatory. These compounds are called aspirin-triggered lipoxins, aspirin-triggered resolvins, and aspirin-triggered maresins.[21]

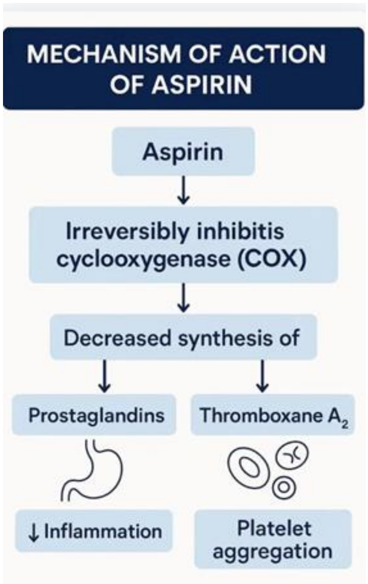


Fig: Aspirin Moa[22]

1.15 New Stratergesis of stoke disease:
Emerging Therapies: Pleiotropic Multi-target Drugs to Treat Stroke Victims

1.15. [1] State-of-the-Art Treatments:

Two drugs used for stroke treatment—tPA (Alteplase®) and edaravone (Radicut®)—work through different mechanisms.
tPA is the only FDA-approved therapy for acute ischemic stroke in the U.S. It dissolves clots by activating plasminogen and can partially or fully reopen blocked vessels in 22–40% of patients, though results vary. It must be given within 3 hours (effective up to 4.5 hours) and is underused, reaching only 2–4% of eligible patients. Limitations include lack of neuroprotective effects and a 3–6% risk of intracerebral hemorrhage. **Edaravone**, approved in Japan, is a free-radical scavenger that provides antioxidant neuroprotection. It can be given within 24 hours of stroke onset and is widely used there, with mixed but generally positive reported benefits. Side effects are usually mild, with reversible acute renal failure being the most notable.[23]

1.15. [2] Time to Treat Victims:

There are two major therapeutic windows for stroke treatment:

- **Acute phase (within 24 hours):**

Interventions aim to block the ischemic cascade early, reducing neuronal damage and behavioral deficits. Early cell death arises from rapid energy failure, impaired microcirculation, excessive glutamate release causing delayed neuronal death, and harmful free radicals that damage brain tissue. These factors threaten the *ischemic penumbra*, a potentially salvageable region. Neuroprotective drugs target this tissue, but most patients miss the narrow time window.[24]

- **Late phase (after 24 hours):**

Neuroprotection is no longer effective, so treatment must focus on promoting neuronal repair and improving functional recovery.

1.15. [3] The Learning Curve:

Developing effective neuroprotective treatments for stroke has been difficult, and many past efforts have failed. Most strategies have relied on monotherapies aimed at a single target—such as free-radical scavengers—but clinical results have been inconsistent. The failure of NXY-059 (partly because it could not cross the blood–brain barrier and was tested beyond its effective time window) highlighted problems in drug design and translation.

Because the ischemic cascade activates many damaging pathways at once in both the core and penumbra, it is unlikely that a single-target drug can provide strong neuroprotection. Therefore, future progress may require multi-target drugs or combination therapies that act on several components of the cascade simultaneously to improve neuroprotection and functional recovery.[25]

1.15. [4] Modeling the Heterogeneity of Stroke:

Stroke drug discovery relies on two modeling levels: **in vitro screens** and **in vivo models**. Traditional in vitro approaches target single enzymes or receptors, but this is inadequate for acute ischemic stroke, which involves many simultaneous damaging pathways. Newer approaches use multiple cell assays to identify multi-target drugs. An example is **STAZN**, a potent free-radical scavenger and multi-target compound shown to protect hippocampal cells from both energy-failure–induced and glutamate-induced cell death, demonstrating the value of broader in vitro screening.

In vivo modeling must also reflect patient heterogeneity. Clinical trial populations span nearly the full NIH Stroke Scale range and include diverse stroke types, all of which respond to tPA. Therefore, heterogeneous animal models—like the rabbit embolic stroke model—are essential for realistic translational testing. Recommendations include using death as an endpoint, avoiding neuroprotective anesthetics that distort results, and including tPA as the gold-standard comparator. Studies in this issue highlight the variability of infarct patterns in unanesthetized rabbit models, which more accurately mirror the diversity seen in human stroke patients.[26]

1.15. [5] Pleiotropic Drug Discoveries:

highlights three emerging multi-target (pleiotropic) drug strategies for stroke treatment:

- **Edaravone :**

Already approved in Japan, edaravone acts through multiple mechanisms: antioxidant effects, suppression of apoptosis, reduced microglia-induced toxicity, inflammation reduction, inhibition of lipid oxidation, decreased edema (via lower aquaporin-4), and reduction of MMP-9 activity. These actions help protect neurons, blood vessels, and behavior after stroke.

- **Curcuminoids (curcumin and CNB-001)**

Curcuminoids also have broad mechanisms: antioxidant, anti-inflammatory, anti-apoptotic effects, protection of the BBB, edema reduction, and enhancement of BDNF and TrkB signaling for neural repair. The designer curcuminoid CNB-001 crosses the BBB more effectively and improves mitochondrial function and behavioral outcomes after stroke.

- **Minocycline**

This drug provides neuroprotection through anti-inflammatory and anti-apoptotic pathways, including inhibition of iNOS, MAP kinase, glutamate toxicity, microglial activation, and caspase-1 activity. It also reduces MMP-9 levels.

Together, these drugs exemplify multi-target therapies that intervene at several points in the ischemic cascade. Curcuminoids may have an added advantage through promoting neuronal repair via trophic factor pathways.[27]

Conclusion :

Stroke is a major global cause of death and disability, but timely recognition and treatment can greatly improve outcomes. Rapid interventions such as IV thrombolysis, mechanical thrombectomy, and early supportive care remain the cornerstone of management. Understanding and controlling risk factors like hypertension, diabetes, and high cholesterol are essential for prevention. Emerging multi-target therapies—including edaravone, curcuminoids, and minocycline—offer promising future strategies for neuroprotection and recovery. Overall, early treatment, prevention, and advanced therapies are key to reducing the burden of stroke.

Reference

1.Adams H.P., Jr., Bendixen B.H., Kappelle L.J., et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke. 1993;24:35–41. – PubMed

2. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV., American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia. Council on Cardiovascular Radiology and Intervention. Council on Cardiovascular and Stroke Nursing. Council on Epidemiology and Prevention. Council on Peripheral Vascular Disease. Council on Nutrition, Physical Activity and Metabolism. An updated definition of

stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Jul;44(7):2064-89

3. https://share.google/pSBjXvaKxh2JUIQ0G

4.https://www.hopkinsmedicine.org/health/conditions-and-diseases/stroke/types-of-stroke

5. Chohan SA, Venkatesh PK, How CH. Long-term complications of stroke and secondary prevention: an overview for primary care physicians. Singapore Med J. 2019 Dec;60(12):616-620.

6. Hoh BL, Ko NU, Amin-Hanjani S, Chou SH-Y, Cruz-Flores S, Dangayach NS, Derdeyn CP, Du R, Hänggi D, Hetts SW, Ifejika NL, Johnson R, Keigher KM, Leslie-Mazwi TM, Lucke-Wold B, Rabinstein AA, Robicsek SA, Stapleton CJ, Suarez JI, Tjoumakaris SI, Welch BG. 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2023 Jul;54(7):e314-e370.

7. Zhang J, Ta N, Fu M, Tian FH, Wang J, Zhang T, Wang B. Use of DWI-FLAIR Mismatch to Estimate the Onset Time in Wake-Up Strokes. Neuropsychiatr Dis Treat. 2022;18:355-361

8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019 Dec;50(12):e344-e418.

9. Widimsky P, Snyder K, Sulzenko J, Hopkins LN, Stetkarova I. Acute ischaemic stroke: recent advances in reperfusion treatment. Eur Heart J. 2023 Apr 07;44(14):1205-1215. [PMC free article] [PubMed] [Reference list]

10. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, Sila CA, Hassan AE, Millan M, Levy EI, Mitchell P, Chen M, English JD, Shah QA, Silver FL, Pereira VM, Mehta BP, Baxter BW, Abraham MG, Cardona P, Veznedaroglu E, Hellinger FR, Feng L, Kirmani JF, Lopes DK, Jankowitz BT, Frankel MR, Costalat V, Vora NA, Yoo AJ, Malik AM, Furlan AJ, Rubiera M, Aghaebrahim A, Olivot JM, Tekle WG, Shields R, Graves T, Lewis RJ, Smith WS, Liebeskind DS, Saver JL, Jovin TG., DAWN Trial Investigators. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2018 Jan 04;378(1):11-21.

11. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019 Dec;50(12):e344-e418

12. oh BL, Ko NU, Amin-Hanjani S, Chou SH-Y, Cruz-Flores S, Dangayach NS, Derdeyn CP, Du R, Hänggi D, Hetts SW, Ifejika NL, Johnson R, Keigher KM, Leslie-Mazwi TM, Lucke-Wold B, Rabinstein AA, Robicsek SA, Stapleton CJ, Suarez JI, Tjoumakaris SI, Welch BG. 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2023 Jul;54(7):e314-e370

13. Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014 Mar 26;2014(3):CD000029

14. Chou R, Cantor A, Dana T, Wagner J, Ahmed AY, Fu R, Ferencik M. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2022 Aug 23;328(8):754-771.
15. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995–2008. *Ann of Neurol*. 2011;70(5):713–721.
16. 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.
17. Caplan LR. Patient information: hemorrhagic stroke treatment. www.uptodate.com/contents/patient-information-hemorrhagic-stroke-treatment. Accessed October 3, 2011.
18. https://share.google/2ebydXRDQLCFtkrSc
19. Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, Kisor DF, Limdi NA, Lee YM, Scott SA, Hulot JS, Roden DM, Gaedigk A, Caudle KE, Klein TE, Johnson JA, Shuldiner AR. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. Clin Pharmacol Ther. 2022 Nov;112(5):959-967.
20. https://pharmacyfreak.com/wp-content/uploads/2025/06/ChatGPT-Image-Jun-23-2025-08_48_19-PM.png
21. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Sep 15, 2024. Willow Bark.
22.https://www.google.com/imgres?imgurl=https://pharmacyfreak.com/wp-content/uploads/2025/05/ChatGPT_Image_May_25_2025_11_40_00_AM.jpg&tbnid=YbMDjZNtiCB4cM&vet=1&imgrefurl=https://pharmacyfreak.com/aspirin-mechanism-of-action/&docid=5Nvq0BSAz6PUKM&w=1024&h=1536&hl=en-IN&source=sh/x/im/m1/4&kgs=d3ade318ebddf02c&shem=damc,isst,shrtsdl&utm_source=damc,isst,shrtsdl,sh/x/im/m1/4
23 Sinha M, Anuradha H, Juyal R, Shukla R, Garg R, Kar A. Edaravone in acute ischemic stroke, an Indian experience. Neurol Asia. 2009;14:7–10.
24.Lapchak PA, De Taboada L. Transcranial near infrared laser treatment (NILT) increases cortical adenosine-5′-triphosphate (ATP) content following embolic strokes in rabbits. Brain Res. 2010;1306:100–5. doi: 10.1016/j.brainres.2009.10.022
25.Shuaib A, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, et al. NXY-059 for the treatment of acute ischemic stroke. N Engl J Med. 2007;357(6):562–71. doi: 10.1056/NEJMoa070240
26.Becker DA. Diagnostic and therapeutic applications of azulenyl nitrone spin traps. Cell Mol Life Sci. 1999;56(7–8):626–33. doi: 10.1007/s000180050457
27.Lapchak PA, Schubert D, Maher P. De-risking of Stilbazulenyl nitrone (STAZN), a lipophilic nitrone to treat stroke using a unique panel of in vitro assays. Transl Stroke Res. 2011;2(2) doi: 10.1007/s12975-011-0071-7. [
28. https://www.nhlbi.nih.gov/health/stroke/symptoms