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A Revised Novel Approach of Ischemic Stroke through Thrombolytic Therapy and Thrombectomy

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Authors' contributions

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Review Article

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ABSTRACT

This comprehensive overview analyses the development of ischemic stroke therapy, emphasizing the critical significance that thrombolytic therapy and thrombectomy techniques have played. With a particular set of difficulties, thrombolytic therapy tissue plasminogen activator, or tPA has revolutionized acute stroke care by breaking up clots in a crucial window of time. Simultaneously, thrombectomy has become a revolutionary intervention, especially for large-vessel occlusions, offering a localized, effective approach and expanding therapy windows. This review guides you through the historical events, technological developments, and continuing research that have shaped these methods. The importance of individualized treatment plans, the use of telemedicine, and the bright future prospects for the management of ischemic strokes are emphasized.

Keywords: Thrombectomy; thrombolytic therapy; ischemic cascade; aspiration catheters; stent retrieval; combined therapy.

1. INTRODUCTION

Ischemic stroke is the most prevalent kind of stroke. When a blood vessel in the neck or brain becomes clogged, it occurs [1]. If a blood clot forms in the brain or neck blood vessels, it is known as thrombosis. If a blood clot travels from another part of the body, such as the heart, it is

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known as embolism [2,3]. If an artery in or moving to the brain is severely narrowed it is known as stenosis [3].

Stroke is the second-leading cause of death and the primary global cause of disability. According to the Global Stroke Factsheet published in 2022, the lifetime risk of having a stroke has increased by 50% in the last 17 years Now, 1 in 4 people is estimated to have a stroke in their lifetime. Incidence of stroke increased by 70%, stroke mortality increased by 43%, stroke prevalence increased by 102%, and Disability Adjusted Life Years (DALY) increased by 143% from 1990 to 2019. The most remarkable aspect is that 86% of stroke-related fatalities and 89% of disability-adjusted life years (DALYs) worldwide occur in low- and middle-income nations.

To prevent brain damage, minimize disability, and save lives, it is crucial to treat ischemic stroke quickly and efficiently [4]. The brain's blood flow can be quickly restored within the right time window, preserving vital brain tissue. This enhances survivors' functional rehabilitation and quality of life while also reducing the psychological and financial strain on them and society. Early stroke treatment is essential for lowering death, avoiding long-term impairment, and enhancing patient outcomes overall.

Thrombolytic therapy, which employs drugs like tissue plasminogen activator (tPA), breaks up blood clots in patients who have ischemic stroke [5]. By the use of specialized tools, thrombectomy, a minimally invasive treatment, physically eliminates clots [6]. Both treatments aim to quickly restore cerebral blood flow, but as their procedures and eligibility criteria differ an accurate evaluation of their roles in stroke therapy is required.

This review article's main objective is to fully evaluate thrombolytic therapy and thrombectomy for ischemic stroke treatments. Examining their methods, clinical results, complications, and relative efficacy are among the objectives. Additionally, we aim to help physicians and researchers make wise decisions by highlighting developments, difficulties, and potential directions in stroke care.

2. PATHOPHYSIOLOGY

Reduced blood and oxygen flow to the brain as a result of inadequate blood flow through blood vessels is known as an ischemic stroke. The internal carotid and vertebral arteries carry blood to the brain [7].

There are two types of ischemic stroke: embolic and thrombotic.

In thrombotic strokes, restricted blood vessels from atherosclerosis cause plaque formation, which can constrict and clog the vessels, resulting in a thrombotic stroke. Due to ulceration and common stenotic plaques in the aortic arch, neck, and cranial vessels, atherosclerosis can also cause emboli in cerebral vessels [8].

Thrombi occur in the lipid cores of plaques exposed in the bloodstream as a result of inflammation and plaque cap ulceration in atherosclerosis. This can constrict blood vessels and result in a stroke.
In embolic strokes, the embolism causes a reduction in blood supply to the brain, which in turn leads to stress, necrosis, and the release of cellular components into the extracellular space, which ultimately ends in the loss of neuronal function [9].

2.1 The Distinction between Embolic and Thrombotic

Thrombosis and embolism are circulatory system blockages that demand rapid medical care. You risk losing vital blood flow, which could deprive you of oxygen and cause an unexpected death, if you don't receive treatment. Both types of obstructions might cause your blood arteries to constrict.

Thrombus

Blood clots in the veins are a medical condition known as deep vein thrombosis (DVT). A thrombus is the term for the blockage that develops. They are located in several bodily areas, such as the arm, pelvis, thigh, and lower leg.

Thrombosis occurs in two primary forms:

1. **Venous thrombosis:** Occurs when a blood clot forms in a vein and blocks blood flow [10].

Typical signs of venous thrombosis consist of:

- Tenderness and pain
- redness or discolouration
- edema, frequently in the foot, ankle, or knee

2. **Arterial thrombosis:** A blood clot forms in an artery that transports blood from and to the heart. A common cause of arterial thrombosis is the hardening of the artery walls due to the accumulation of fat and calcium deposits. Plaque forms as a result, which has the potential to burst at any time and produce a blood clot [11].

Symptoms of arterial thrombosis including:

- Chest pain that happens at random, such as during resting, and that does not respond to therapy
- shortness or loss of breath
- sweating
- nausea
- a limb or region of skin that has turned chilly, lighter than usual, and extremely uncomfortable
- inexplicable reduction of muscle strength
- the face's lower half slumps to one side

Embolism

Pulmonary embolism: A blockage in one of your lung arteries causes a pulmonary embolism (PE). They frequently occur when a blood clot separates from a deep vein thrombosis and travels through the bloodstream and into your lungs [11].

Common symptoms of PE include:

- trouble breathing
- rapid breathing
- dizziness and light-headedness
- rapid heart rate
- chest pain that gets worse when breathing in
- coughing up blood
- passing out

2.2 Ischemic Cascade

When blood flow is insufficient, an ischemic cascade occurs, which is a set of Biochemical reactions in the brain and other oxygen-dependent tissues [12]. This series includes:

1. Excitotoxicity: When neurons lack energy, they produce too many neurotransmitters, such as glutamate, which overstimulates receptors and causes an influx of calcium, further harming cells [13].
2. Free Radical Production: Ischemia causes the production of free radicals, which are reactive chemicals that can damage DNA, proteins, and cell membranes, leading to oxidative stress and neuronal injury [14].
3. Inflammation: Ischemia causes the brain to go into an inflammatory state that may worsen tissue damage by activating immune cells and releasing chemicals that promote inflammation [15].
4. Cell Death: Prolonged ischemia can result in two types of cell death:

- Necrosis: Acute ischemia and excitotoxicity can cause certain neurons to directly die.
- Apoptosis: Energy deprivation, excitotoxicity, and oxidative stress work together to cause the programmed cell death, or apoptosis, of other neurons.

2.3 Formation of Thrombi and Emboli

When a blood vessel gets impared, platelets bind to collagen and activate it. Catalytic support is required for a biochemical reactions that results in the production of thrombin [16]. There are multiple steps in this process:

1. Vasoconstriction: The narrowing of blood vessels.
2. Platelet Plug Formation: At the location, platelets clump together.
3. Coagulation Cascade Activation: This initiates the coagulation process.
4. Formation of Fibrin Plug: A firm clot occurs.

Over time, the clot may grow, dissolve, and break into smaller pieces known as emboli, These pieces can then pass through the bloodstream and reach different areas of the body.

2.4 TOAST Classification of Ischemic Stroke

There are five categories in the TOAST classification system:1) large-artery atherosclerosis, 2) cardioembolism, 3) small-artery occlusion (lacune), 4) stroke of other determined etiology, and 5) stroke of undetermined etiology [17,18].

1) large-artery atherosclerosis

Individuals diagnosed with large-artery atherosclerosis exhibit clinical and imaging manifestations, including major brain arteries or cortical branches blockage or stenosis (>50%), which is most likely caused by atherosclerosis.

Brain stem/cerebellar dysfunction or cerebral cortical impairment (such as aphasia or neglect) are examples of clinical presentations. The diagnosis is supported by historical indicators such as decreased pulses, carotid bruit, transient ischemic attacks (TIAs), and intermittent claudication. Large-artery atherosclerotic origin is suggested by lesions larger than 1.5 cm in cortical/cerebellar areas and brain stem/subcortical hemisphere infarcts. Support is provided by duplex imaging or arteriography showing more than 50% stenosis in a significant intracranial or extracranial artery. Cardiogenic embolism must be ruled out for the diagnosis. It is difficult to confirm a stroke caused by large-artery atherosclerosis if duplex/arteriographic scans show no abnormalities or only minor changes.

2) cardioembolism

Patients with artery occlusions most likely brought on by a cardiac embolus are considered to have cardioembolism. Cardiac sources are classified as high-risk or medium-risk based on their proclivity for embolism. For a diagnosis of cardioembolic stroke to be made, at least one cardiac cause must be identified. The imaging and clinical results are similar to those of atherosclerosis of the major arteries. A clinical diagnosis of cardiogenic stroke is supported by a history of prior TIA/stroke in various vascular regions or systemic embolism. It is important to exclude out large-artery atherosclerotic origins. A potential cardioembolic stroke occurs when a patient has a stroke with a medium-risk cardiac source and no other cause.

3) small-artery occlusion (lacune)

Strokes caused by small-artery occlusion, or lacunar infarcts, are commonly referred to as such. Individuals display classic lacunar syndromes without any indication of cerebral cortical damage. The diagnosis is supported by a history of hypertension or diabetes mellitus. A normal CT/MRI scan or a subcortical hemispheric lesion with a diameter of less than 1.5 cm should be visible on imaging. A major extracranial arterial evaluation shouldn't show a stenosis of more than 50% in an ipsilateral artery, nor should it indicate the presence of any potential cardiac sources for embolism.

4) stroke of other determined etiology

Rare reasons such as nonatherosclerotic vasculopathies, hypercoagulable conditions, or hematologic diseases can be attributed to acute stroke of other identified etiology. Regardless of size or location, patients must exhibit clinical and CT/MRI evidence of acute ischemic stroke. Diagnostic procedures like arteriography or blood tests ought to identify these odd reasons. Further research is necessary to rule out cardiac origins of embolism and large-artery atherosclerosis.

5) stroke of undetermined etiology

Cases of stroke with an unknown etiology include those in which the cause cannot be determined with certainty. Even after thorough examination, some patients still have no probable reason, while others have quick assessments but no cause found. Patients in this category may have two or more possible reasons, which complicates the process of reaching a conclusive diagnosis. For example, a patient with a medium-risk cardiac embolism source and another potential cause would be categorized as having an unknown etiology. Patients with classic lacunar syndrome with 50% ipsilateral carotid stenosis, or those with atrial fibrillation and 50% ipsilateral stenosis, are two examples.

3. THROMBOLYTIC THERAPY

In thrombolytic therapy, tissue plasminogen activators (TPA) are utilized. TPA, commonly referred to as alteplase, is a drug used to treat ischemic strokes; it works by dissolving blood clots. via plasminogen activation, which causes platelets to aggregate into fibrin. In particular, the fibrin cleaves the zymogen plasminogen at the arg561-val562 peptide bond to generate plasmin [19]. A binding site is provided for both plasminogen and TPA. Being an endogenous fibrinolytic, plasmin dissolves clots by breaking the crosslinks between the fibrin molecules supporting them. Plasmin is short-lived because alpha2 antiplasmin, an abundant plasmin inhibitor, inactivates and restricts plasmin at the site of clot formation [5].

Furthermore, Plasminogen activator inhibitor 1 (PAI-1) binds to TPA, generating an inactive complex that is then cleared from circulation by the liver via the scavenging receptor LDL receptor-related protein 1 (LRP1).

Neuroserpin works similarly to LRP1 and PAI-1 in the nervous system to eliminate TPA from the body [20].

Common Thrombolytic Medication:

1. **Alteplase:** is a commonly used thrombolytic medication. It is frequently used to treat ischemic stroke, pulmonary embolism, and acute myocardial infarction.
2. **Reteplase:** Used to treat acute myocardial infarction, reteplase works similarly to alteplase. It will be administered as a bolus injection.
3. **Tenecteplase:** This thrombolytic is a modified version of alteplase, which has a longer half-life and is therefore less complicated to administer [21].

3.1 The History and Development of Thrombolytic Therapy

The history of thrombolytic therapy began in 1933 when Tillet and Garner discovered that certain strains of streptococcus could dissolve fibrin clots. The streptococci clumped together in the presence of human serum but not plasma, highlighting the function of fibrinogen, leading to this accidental finding. Recombinant tissue plasminogen activator development yielded significant advancements in the 1980s [22]. A significant turning point in thrombolytic therapy was reached in the 1990s with the FDA's approval and clinical studies. It effectively broke up blood clots, revolutionizing stroke care. However, prompt delivery and cautious patient selection are essential to this treatment's success.

3.2 Patient Selection and Eligibility Criteria

AHA/ASA guidelines state that if a patient fulfils the following requirements, they can receive thrombolytic therapy within a window of three to four hours [23]:

1. Below the age of 80.
2. Not using anticoagulants orally.
3. Has a baseline score of less than 25 on the National Institutes of Health Stroke Scale (NIHSS).
4. No history of diabetes or stroke.
5. No imaging data indicating that more than one-third of the middle cerebral artery region has been damaged by ischemia [24].

3.3 Dosing and Protocols for Administration

Before utilizing tPA, the only blood test required is to check blood glucose levels. It could be necessary to perform additional tests like PT, PTT, and INR if the patient is on anticoagulants like coumadin [25]. The duration has a significant impact on tPA's efficacy. The better the results, the earlier a patient receives tPA.

90 mg is the maximum recommended dose. Patients weighing 100 kg or fewer get 90% of the 0.9 mg/kg dose as a continuous 60-minute infusion, with 10% of the dose administered as an IV bolus over one minute. Patients who weigh more than 100 kg are given an IV bolus of 10% of the 90 mg dose over the course of one minute, and the remaining 90% is given continuously for 60 minutes [26].

3.4 Clinical Outcomes and Efficacy

When given in a timely manner, thrombolytic treatment for ischemic stroke considerably improves clinical outcomes by decreasing disability and promoting functional recovery. Although its effectiveness is well established, it necessitates cautious patient selection and adherence to the recommended treatment protocols [27].

3.5 Risk and Complications Including Bleeding Events

There is a chance of bleeding incidents when using thrombolytic therapy for ischemic stroke, especially cerebral hemorrhage. These problems are extremely concerning and have the potential to be life-threatening [28]. To reduce these risks and maximize the benefits of treatment, it is crucial to carefully select patients, follow time-sensitive protocols, and conduct continuous monitoring.

3.6 Role in Acute Stroke Management and Time-Sensitive Considerations

Because it quickly restores blood flow, thrombolytic treatment is essential to the management of acute stroke patients [29]. It is important to recognize and treat stroke symptoms as soon as possible because the treatment has a limited window of time (about 4.5 hours from the onset of symptoms) in order to be most effective [30].

4. THROMBECTOMY

The mechanical thrombectomy is a minimally invasive process that can be used to remove

clots from blood vessels. A neuroradiologist uses specialized equipment to reach clogged brain blood vessels during mechanical thrombectomy [6]. Under fluoroscopic supervision, a tiny incision is made in the wrist or groin, and a catheter is introduced into the blood vessel. In order to break the clot, a stent-like device called a stent retriever is inserted via the catheter. The stent retriever widens the vessel, capturing the clot, which is subsequently removed [31]. This process removes the clot blocking the blood vessel, preventing or minimizing brain damage. MRIs and CT scans are some of the imaging methods used to evaluate patients before mechanical thrombectomy. The surgery is usually completed in 6 to 24 hours. Tissue plasminogen activator may be utilized in addition to mechanical thrombectomy if patients arrive within 4.5 hours of the procedure [32].

4.1 Historical Development and Technological Advancements of Thrombectomy

The history of thrombectomy has experienced remarkable advancement. Early attempts to develop clot-removal catheters encountered technical difficulties in the 1980s and 1990s. However, the invention of stent retrievers in the early 2000s changed the game. Particularly for large-vessel occlusions such as those in the middle cerebral artery, these devices significantly enhanced the retrieval of clots. From the late 2000s to the present [33], there have been continuous developments in clot imaging, improved stent retrievers, and the creation of specialized stroke centers and thrombectomy teams.

Modern thrombectomy technology has completely changed the way stroke patients are treated. Since stent retrievers are highly effective and require less intrusive surgery, they are now the preferred option for clot removal. Suction-based aspiration catheters are useful for complex situations and convoluted arteries. Perfusion imaging and 3-D angiography are examples of advanced imaging that improves patient selection and accurate clot targeting [34]. Underserved patients can receive expert consultations by use of telemedicine services. Accurate navigation inside the circulatory system is ensured via guiding catheters. From identification to retrieval, the entire thrombectomy procedure is streamlined by integrated systems. Innovative tools and methods are being investigated in ongoing studies and clinical trials to improve thrombectomy operations' efficacy and safety.

4.2 Patient Selection Criteria, Including Considerations for Extended Time Windows

In certain cases, thrombectomy may be necessary up to 16 hours after the onset of symptoms or the last time an unwitnessed stroke was well-documented [35,36].

Several considerations are taken into account while choosing patients for extended duration of thrombectomy:

1. Time Window: Although the typical treatment window is 6 hours, some patients may be eligible in less time, particularly if imaging results are encouraging.
2. Imaging: Advanced techniques like as perfusion imaging helps in the identification of brain tissue that can be spared, which aids in patient selection [37].
3. Clot Location: The location of the clot is important; those in crucial vessels such as the middle cerebral artery may have a better chance.
4. Clinical Assessment: Eligibility is determined by assessing the patient's condition, including any neurological impairments.
5. Risk vs. Benefit: It's important to weigh the potential advantages against the hazards, particularly for patients who are not inside the typical time range [32].

4.3 Devices

Thrombectomy involves the use of a variety of devices, including guide catheters, stent retrievers, microcatheters, aspiration catheters, and aspiration pump systems.

- Aspiration Catheters: These big catheters draw blood clots out using negative pressure suction. The anatomy of the patient and the placement of the clot determine which catheter is best; their relative efficacy for myocardial infarction (MI) is yet unknown [38].
- Aspiration Pump: To remove clots, negative pressure is created using an aspiration pump equipment or a 16–20 mL syringe.
- Microcatheters/Guidewires: Small catheters that are contained inside of a larger catheter and are guided by a wire to treat

complicated occlusions of the coronary and peripheral blood arteries [39].

- Stent Retrieval Tool (Solitaire): This tool deploys an expandable stent, secures it to the clot, and removes the clot. Research revealed no appreciable variation in the safety or effectiveness of the two stent retrieval systems. The first gadget approved to treat symptoms up to 24 hours after onset is another stent retriever [38].

4.4 Procedure

The steps are usually as follows:

1. Medication and preparation: The patient puts on a hospital gown and is given an IV in their arm.
2. Anaesthesia: Medical practitioners use a local anaesthetic to numb the access site so the patient is unaware of the incision, which is typically made in the arm, neck, or groin.
3. Clot removal: A surgeon directs a device known as a stent retriever to the obstruction by threading it through the catheter. The surgeon will draw the clot backwards to remove it once the stent has caught it.
4. Stent placement: Following clot removal, the surgeon will press through the clot to maintain the artery open. The stent will then be implanted.
5. Closing and cleaning: The surgeon seals the blood vessels and takes out the tools that are used. The incision site is then bandaged or stitched [6,40].

4.5 Complication

Although thrombectomy is a useful treatment for eliminating blood clots, there may be problems. Blood vessel tearing, heavy bleeding, blood vessel damage or narrowing, significant bruising at the puncture site, bleeding in the brain, infection, and anaesthesia-related adverse responses are some examples of these issues [41]. When contemplating a thrombectomy as a course of treatment, patients should be informed of these possible dangers and talk about them with their medical professionals.

Table 1. Relation between thrombolytic therapy and thrombectomy

	thrombolytic therapy	**thrombectomy**
Mechanism of action	It involves giving medications to the patient, such as tPA, which dissolve blood clots by changing plasminogen into plasmin. It has a systemic effect on clots throughout the body [42].	a minimally invasive procedure where a device, typically a stent retriever or aspiration catheter, is used to physically remove the clot from the blocked blood vessel. It's a more localized and targeted approach [43].
Patient selection	The start of symptoms determines patient eligibility, with stringent time limits. It might not be a suitable fit for patients who have bleeding problems or who recently underwent surgery [44].	Based on the location, burden, and quantity of potentially salvageable brain tissue, imaging evaluations, such as CT or MRI scans, are employed in the patient selection process to identify appropriate candidates [45].
Safety profile	involves a risk of bleeding, particularly cerebral haemorrhage, which can be deadly. To reduce this danger, eligibility requirements are stringent [46].	Since the procedure is restricted, there is less chance of bleeding issues. However, there is a chance of problems, so proceed with caution [47].
Efficacy	When given within the first few hours after the onset of symptoms, usually within a window of up to 4.5 hours, it is effective.	Effective in some individuals with specific imaging characteristics lasting at least 24 hours
Benefits	• Rapid treatment within 4.5 hours of symptom onset can be lifesaving. • The course of treatment is widely accepted and well-established [48].	• Very successful in treating large-vessel occlusions • Lower risk of bleeding problems [49].
Limitations	• Time-sensitive • Increased risk of bleeding complications	• Higher resources • Smaller clots may have less effectiveness.

5. COMPARATIVE ANALYSIS BETWEEN THROMBOLYTIC THERAPY AND THROMBECTOMY

5.1 Combined Therapy

When a patient is eligible, especially if they have a large-vessel blockage, a combination of thrombolytic treatment and thrombectomy may be indicated; the patient's condition, the treatment window, and the available resources may all determine which of the two methods is used [50].

6. CHALLENGES AND FUTURE DIRECTIONS

Even with the advancements, there are still a number of aspects of stroke treatment that require attention. As was previously said, more research will clarify the function of EVT in massive infarcts. To investigate this matter, two trials are presently in progress: Endovascular Therapy for Low NIHSS Ischemic Strokes (ENDOLOW, NCT04167527) and Minor Stroke Therapy Evaluation (MOSTE, NCT03796468).

Regarding thrombolytic therapy, there are currently three ongoing trials: Safety and Efficacy of Levofloxacin Combined With Intravenous Thrombolysis for Acute Ischemic Stroke (NCT05741905), Platelet Function in Patients With Ischemic Stroke Treated With Anti-thrombotic or Thrombolytics (NCT05415150), and Tenepteplase Thrombolytic Therapy for Acute Ischemic Stroke in China (TTT-AIS CHINA, NCT06078995).

Regarding thrombectomy, two clinical trials are currently underway: The TESLA Trial: Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke (TESLA, NCT03805308), which will be finished by the end of the year, and the Taiwan Registry of Endovascular Thrombectomy for Acute Ischemic Stroke (TREAT-AIS, NCT05281055).

6.1 Future Directions and Research in Ischemic Stroke

Stroke care could undergo a transformation thanks to upcoming studies on ischemic stroke. Results will be enhanced by prolonged thrombectomy time windows, neuroprotection tactics, AI-driven diagnostics, and personalized therapy. Improvements in neuroregeneration and rehabilitation could lead to better healing [51]. The burden of stroke will be decreased via neuroinflammation regulation, prevention techniques, and telestroke programs. Better patient care will be ensured by innovation driven by telemedicine, healthcare network development, and collaborative clinical trials.

6.2 Emerging Therapies and Potential Game-Changers

Innovative thrombolytics, precision medicine, stem cell-based therapeutics, and neuroprotective medicines are among the promising new treatments for ischemic stroke. The field of stroke care is evolving thanks to telemedicine, AI-driven diagnosis, and remote monitoring. Treatment windows are expanded by novel devices and approaches in thrombectomy [52]. Neuroregeneration techniques and combination medicines have the potential to completely change how strokes are managed, minimizing disability and enhancing patient outcomes.

7. CONCLUSION

The extensive review of thrombolytic therapy and thrombectomy techniques highlights the remarkable advances in the treatment of ischemic stroke. Acute treatment was revolutionized by thrombolytic therapy, which was made possible by the innovative function of tPA. However, it was not without its obstacles. including limited eligibility criteria and bleeding hazards. Simultaneously, thrombectomy became an innovative approach, especially for large-vessel occlusions, providing a targeted, efficient intervention and enhancing therapy windows. The changing environment highlights the value of individualized care, continuous research, and telemedicine integration. Future advancements in treatment options, accessibility, and innovation are expected to improve the prognosis for ischemic stroke victims.

CONSENT AND ETHICAL APPROVAL

It is no applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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