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## Literature Review: Thrombolysis In Patients With Acute Ischemic Stroke

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### Abstract

Stroke is one of the leading causes of morbidity and mortality worldwide, with ischemic stroke being the most common type. Ischemic stroke occurs due to obstruction of blood flow to brain tissue, resulting in ischemia, hypoxia, and potentially irreversible brain tissue damage if not treated promptly and appropriately. In the acute phase, the primary principle of management is to restore blood flow to hypoperfused areas of the brain as quickly as possible in order to preserve viable brain tissue, particularly the ischemic penumbra. One of the main reperfusion modalities is thrombolytic therapy, which aims to lyse intravascular thrombi and restore cerebral blood flow. Although thrombolytic therapy provides benefits in improving functional outcomes, it carries a risk of complications, particularly intracranial hemorrhage; therefore, appropriate patient selection, imaging evaluation, and monitoring are required. This final assignment uses a literature review method by examining various sources that discuss thrombolytic therapy in patients with acute ischemic stroke. The literature reviewed covers ischemic stroke, the mechanism of action of thrombolytic agents, methods of administration, inclusion and exclusion criteria, intravenous and intra-arterial thrombolysis, mechanical thrombectomy, types of thrombolytic agents, imaging prior to thrombolysis, as well as complications and therapeutic monitoring. Relevant literature was subsequently reviewed and descriptively organized to provide a comprehensive overview of the role of thrombolysis in the management of acute ischemic stroke. Based on the literature review, thrombolysis plays a role in restoring cerebral blood flow through thrombus lysis. Intravenous alteplase is one of the main therapies that provides optimal benefits when administered as early as possible to patients who meet the appropriate criteria. Patient selection, brain imaging, and monitoring are necessary to reduce the risk of complications, particularly intracranial hemorrhage. Thrombolysis is an important reperfusion therapy for acute ischemic stroke. Prompt and appropriate administration in patients who meet the criteria can improve functional outcomes, while taking into consideration the risk of bleeding and the need for close monitoring.

**Keywords:** Acute Ischemic Stroke, Thrombolysis, Alteplase.

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## INTRODUCTION

Stroke is one of the leading causes of morbidity and mortality worldwide, with ischemic stroke being the most commonly occurring type. This condition results from the obstruction of blood flow to brain tissue, leading to ischemia and hypoxia and potentially causing irreversible brain tissue damage if not treated promptly and appropriately. The burden of stroke is reflected not only in its high mortality rate but also in the long-term disability it causes, which has a substantial impact on patients' quality of life and healthcare systems (Rilianto, 2016; World Stroke Organization, 2022).

In the acute phase of ischemic stroke, the primary principle of management is to restore blood flow to the hypoperfused areas of the brain as rapidly as possible in order to preserve viable brain tissue, particularly within the ischemic penumbra. Delayed reperfusion may lead to expansion of the infarct area and deterioration of neurological outcomes. Therefore, reperfusion strategies constitute a key component of the management of acute ischemic stroke (Abdullah et al., 2024).

Thrombolytic therapy is one of the principal reperfusion modalities for acute ischemic stroke, aimed at lysing intravascular thrombi and restoring cerebral blood flow. The administration of thrombolytic agents, particularly intravenous alteplase, has been demonstrated to significantly improve functional outcomes when administered within the appropriate therapeutic time window following symptom onset. With advances in

technology and an improved understanding of stroke pathophysiology, thrombolytic therapy has evolved beyond the intravenous route to include intra-arterial administration, either as a standalone therapy or as an adjunctive treatment during mechanical thrombectomy procedures (Baig & Bodle, 2023; Utomo, 2022).

Despite its significant therapeutic benefits, thrombolytic therapy carries potential risks. The most serious complication is intracranial hemorrhage; therefore, careful patient selection, appropriate imaging assessment, and intensive post-treatment monitoring are essential components of its implementation. Accordingly, a comprehensive understanding of the indications, mechanisms of action, routes of administration, contraindications, and complications of thrombolytic therapy is essential to maximize its therapeutic benefits while minimizing risks in patients with acute stroke (Rilianto, 2022; Fitriyani et al., 2024).

## RESULTS AND DISCUSSION

### Stroke

#### Definition

Stroke is a sudden or rapidly developing disturbance of brain function characterized by the onset of focal or global neurological deficits lasting for more than 24 hours and not attributable to non-vascular causes. This condition results from abnormalities in cerebral circulation, either due to vascular occlusion (ischemic stroke) or rupture of blood vessels (hemorrhagic stroke). Clinically, stroke may produce various symptoms depending on the affected area of the brain, and its outcomes may include complete recovery, recovery with residual disability, or death. Stroke encompasses conditions such as intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction, all of which are associated with cerebrovascular disorders (Rilianto, 2016).

Ischemic stroke is the most common type of stroke, accounting for approximately 88% of all stroke cases. This condition occurs due to obstruction of cerebral blood vessels, resulting in interruption of blood flow to part or all of the brain tissue. Such obstruction generally results from atherothrombosis involving large or small cerebral blood vessels or from emboli that occlude cerebral arteries. Ischemic stroke frequently occurs during or following prolonged periods of rest, such as upon awakening, and is not accompanied by bleeding. As a consequence of interrupted blood flow, brain tissue becomes ischemic, leading to hypoxia that may subsequently develop into secondary edema and brain cell damage (Rilianto, 2016).

#### Epidemiology

Stroke is a global health problem with an increasing incidence. Data from the *World Stroke Organization* indicate that approximately 12.2 million new stroke cases occur worldwide each year. The most significant increase in stroke incidence has been observed in low- and middle-income countries, where its prevalence has more than doubled and accounts for approximately 89% of stroke-related deaths and disabilities (WSO, 2022). Demographically, stroke occurs more frequently in males than in females, with approximately 89.9% of cases classified as ischemic stroke and 10.1% as hemorrhagic stroke. Stroke is also one of the leading causes of global morbidity and mortality, with an estimated 5.7 million deaths and approximately 50 million cases of disability each year. In Indonesia, stroke was recorded as the leading cause of death in 2018. The fact that this figure has not shown substantial improvement since 2000 indicates that stroke management and healthcare services still require continuous improvement (Abdullah et al., 2024).

#### Classification

Based on its clinical course, stroke can be classified into several forms, namely *Transient Ischemic Attack* (TIA), *Reversible Ischemic Neurologic Deficit* (RIND),

progressing stroke, resolving stroke, and completed stroke. In addition, based on the location and mechanism of vascular occlusion, ischemic stroke can be classified into embolic and thrombotic stroke.

Embolic stroke occurs when cerebral blood vessels are obstructed by materials such as blood, fat, or air, which commonly originate from a thrombus in the heart that becomes dislodged and subsequently occludes a cerebral artery. The embolic process occurs rapidly, with symptoms developing within less than 10–30 seconds. In this type of stroke, the source of the embolus does not originate from the cerebral blood vessels but from another organ, particularly the heart or systemic vascular system. Cardiogenic embolism may occur in various cardiac conditions, including right-to-left cardiac shunts, mitral valve disease resulting from rheumatic heart disease, atrial fibrillation, acute myocardial infarction, and emboli originating from the pulmonary veins. These conditions may reduce cardiac output, resulting in stroke attacks that frequently occur during physical activity (Ramadhani et al., 2023).

Thrombotic stroke occurs due to the formation of a blood clot within a blood vessel supplying the brain. This type can be divided into large-vessel stroke, including involvement of the carotid arterial system, which accounts for approximately 70% of non-hemorrhagic stroke cases caused by thrombosis, and small-vessel stroke involving the circle of Willis and posterior circulation. Thrombosis of small blood vessels generally occurs as a result of impaired blood flow and is frequently associated with hypertension, while also serving as an indicator of atherosclerotic disease. Thrombus formation within an occluded blood vessel causes ischemia of brain tissue, which may result in surrounding edema and congestion. Several conditions that may trigger cerebral thrombosis include atherosclerosis or arteriosclerosis, hypercoagulable states, and arteritis (Ramadhani et al., 2023).

### **Clinical Manifestations**

The signs and symptoms of stroke vary considerably and depend on the severity of the vascular disturbance and the location of the affected brain region. In general, stroke may cause neurological symptoms such as hemiparesis or sudden weakness on one side of the body, sensory disturbances, altered mental status, aphasia, dysarthria, visual disturbances, ataxia, vertigo, nausea, vomiting, and headache. In ischemic stroke, commonly observed symptoms include severe sudden-onset headache, dizziness, confusion or disorientation, blurred vision, difficulty speaking, slurred speech, and impaired balance (Utomo, 2022).

Based on the type of symptoms, their time of onset, and the pattern of complaints, the location of brain tissue damage and the type of stroke can be estimated. For example, weakness or numbness on the right side of the body indicates involvement of the left cerebral hemisphere, whereas impaired balance may suggest involvement of the cerebellum. In general, symptoms of ischemic stroke develop gradually, with relatively preserved consciousness, except when caused by a cardiac embolus, in which symptoms may develop very suddenly and are often accompanied by headache. The level of consciousness in stroke patients can also be assessed using the Glasgow Coma Scale (GCS), in which a score of 3–8 indicates coma, a score of 9–14 indicates confusion, lethargy, or stupor, and a score of 15 indicates full consciousness with an attentive and oriented state (Utomo, 2022).

### **Pathogenesis and Pathophysiology**

Obstruction of the blood vessels supplying the brain may result from several factors, including atherosclerotic lesions, cardiac embolism, and abnormalities of small arteries undergoing fibrinoid degeneration. These conditions can reduce cerebral blood flow and ultimately result in ischemia. Consequently, ATP depletion, disruption of the structural integrity of brain tissue, and the release of cytokines from microglia, astrocytes, endothelial cells, and neurons may occur. Reduced ATP levels impair the function of the  $\text{Na}^+/\text{K}^+$  ion pump, resulting in intracellular water accumulation and the development of cytotoxic edema.

At the same time, this process may stimulate astrocytes to release the neurotransmitter glutamate, which activates proteases, lipases, and nucleases. These enzymes generate metabolic products, including free oxygen radicals, which cause neuronal cell damage and eventually lead to cell death (Ramadhani et al., 2023).

Disruption of the structural integrity of brain tissue may also contribute to cytotoxic edema through rupture of the blood–brain barrier. The resulting edema may compress the surrounding neural tracts, including the motor tracts. Cytokine release can activate, recruit, and promote the adhesion of white blood cells (WBCs) to the endothelial surface, thereby causing further vascular obstruction. Collectively, these mechanisms can impair the function of the motor tracts responsible for controlling movement of the upper and lower extremities, namely the anterior and lateral corticospinal tracts. Consequently, the transmission of neural impulses from the cortex to the subcortical regions is reduced, resulting in decreased neural impulses to the extremity muscles and ultimately causing motor weakness (Ramadhani et al., 2023).

### **Management**

General management of stroke includes airway and breathing stabilization, hemodynamic stabilization, an initial general physical examination—including blood pressure, cardiac, and preliminary neurological assessments—management of increased intracranial pressure, treatment of hemorrhagic transformation, seizure control, temperature management, and supporting examinations such as electrocardiography (ECG) and computed tomography (CT) scanning. The fundamental principle of ischemic stroke management is to restore blood flow to the infarcted area as rapidly as possible without causing intracerebral hemorrhage. The objectives of stroke therapy are to improve cerebral blood perfusion, facilitate clot lysis and prevent further thrombosis, preserve viable brain tissue, and prevent other forms of secondary injury (Rilianto, 2016).

### **Thrombolysis**

#### **Definition**

Thrombolytic therapy, also known as fibrinolytic therapy, is a treatment intended to dissolve harmful intravascular blood clots in order to prevent ischemic injury by restoring blood flow. Thrombolytic agents belong to the plasminogen activator group and are used in various thromboembolic conditions, including acute myocardial infarction, deep vein thrombosis, pulmonary embolism, acute ischemic stroke, acute peripheral arterial occlusion, indwelling catheter occlusion, and intracardiac thrombus formation (Baig & Bodle, 2023). Reperfusion refers to the restoration of circulation to an area affected by ischemia or vascular obstruction. When cerebral blood vessels become occluded or following a period of perfusion deficit, the body attempts to compensate through reperfusion, characterized by increased blood flow to the ischemic region through regional vasodilation or adjustment of vascular reactivity according to cellular metabolic requirements. The benefits of thrombolysis in patients with acute ischemic stroke include reducing disability, lowering mortality, reducing overall healthcare costs, improving quality of life, and promoting patient independence following stroke (Abdullah et al., 2024).

Thrombus formation is a physiological defense mechanism that prevents excessive bleeding following vascular injury and is regulated by antithrombotic mechanisms and endogenous fibrinolysis. However, thrombi that form in the absence of vascular injury and obstruct blood flow are considered pathological. Hypercoagulable states, whether inherited or acquired, may trigger abnormal intravascular thrombus formation, which can subsequently progress to complete luminal occlusion or become detached and cause embolization in distal blood vessels (Baig & Bodle, 2023). Ischemic stroke occurs as a consequence of hypoperfusion in the cerebral penumbra, resulting in hypoxia and temporary loss of neurological function. If the occluded blood vessel is not promptly recanalized,

permanent and irreversible necrosis may occur. The site of vascular occlusion therefore represents the target of thrombolytic therapy, with the objective of restoring blood flow to the hypoperfused area and improving the patient's neurological deficits (Fitriyani et al., 2024).

### **Mechanism of Action**

Hemostasis and thrombosis are processes involving interactions among coagulation factors, blood vessels, and platelets. During thrombosis, activated platelets contribute to the conversion of prothrombin into active thrombin. Thrombin subsequently converts fibrinogen into fibrin, which forms a fibrin mesh or matrix that serves as the structural basis of a blood clot. The body also possesses an endogenous clot-dissolving system involving plasmin, which is derived from plasminogen and acts within the fibrin matrix. Tissue plasminogen activator (tPA) is a naturally occurring fibrinolytic agent produced by vascular endothelial cells and has a high affinity for fibrin. By binding to fibrin and plasminogen at the site of the thrombus, tPA facilitates the conversion of plasminogen into plasmin, thereby enabling degradation of the blood clot (Baig & Bodle, 2023).

Based on their mechanisms of action, thrombolytic agents are classified into two groups: fibrin-specific agents and fibrin-nonspecific agents (Baig & Bodle, 2023).

### **Fibrin-specific agents**

These agents generally require the presence of fibrin for activation, although they can also act in the absence of fibrin to a minimal extent. Examples include alteplase (tPA), reteplase (recombinant plasminogen activator [r-PA]), and tenecteplase.

### **Fibrin-nonspecific agents**

These agents do not require the presence of fibrin for activation and can therefore exert their effects systemically. An example is streptokinase.

Streptokinase was the first thrombolytic agent used clinically and is derived from certain strains of *Streptococcus* bacteria. Another agent is urokinase, a fibrinolytic agent originally identified in human urine. Urokinase is non-antigenic and can directly convert plasminogen into plasmin. Both agents act relatively independently of the presence of local fibrin; therefore, their effects are more systemic and may increase the risk of bleeding (Baig & Bodle, 2023). In contrast, alteplase (tPA) is a recombinant tissue-type plasminogen activator that is structurally identical to naturally occurring tPA and is produced using recombinant DNA technology from a human melanoma cell line. Reteplase (r-PA) is a modified form of tPA produced using *E. coli*. It is non-glycosylated and has more rapid clearance due to the role of the kringle-1 domain. Meanwhile, tenecteplase (TNK-tPA) is a tPA variant containing three point mutations and has a slower clearance rate, allowing administration as a simpler single intravenous bolus (Baig & Bodle, 2023).

Fibrinolytic therapy in acute ischemic stroke aims to dissolve blood clots that obstruct cerebral blood flow, thereby restoring perfusion to brain tissue that has not yet undergone infarction. According to the guidelines of the *American Heart Association* (AHA), intravenous alteplase (tPA) is a principal thrombolytic therapy for acute ischemic stroke and has been demonstrated to significantly improve functional outcomes when administered within 4.5 hours of stroke onset. Therefore, patients with acute ischemic stroke who present within 4.5 hours of the time they were last known to be well and who have no absolute contraindications are recommended to receive intravenous alteplase (tPA). The therapeutic benefit is greatest when treatment is administered as early as possible after stroke onset and decreases with increasing time to treatment (Baig & Bodle, 2023).

### **Route of Administration**

Thrombolytic agents can be administered through two main routes: systemically through peripheral intravenous (IV) infusion or locally through direct delivery to the site of the blood clot using a catheter following navigation to the target location. One developing

approach is *ultrasound-assisted catheter-directed thrombolysis* (USCDT), which has been shown to potentially improve the efficacy and safety of thrombolytic therapy. Thrombolytic agents, also referred to as fibrinolytic agents or plasminogen activators, are essentially serine proteases that function by converting plasminogen into active plasmin, thereby facilitating fibrin degradation within the blood clot (Baig & Bodle, 2023).

### **Inclusion and Exclusion Criteria**

Not all cases of ischemic stroke are eligible for thrombolytic therapy. When eligibility criteria are fulfilled, patients with acute ischemic stroke should receive intravenous (IV) alteplase (r-tPA). The inclusion criteria for thrombolytic therapy include the following (Fitriyani et al., 2024):

1. Diagnosis of ischemic stroke with a clinically significant neurological deficit.
2. Treatment can be administered within 4.5 hours of symptom onset.
3. Age  $\geq 18$  years.

Meanwhile, several exclusion criteria for thrombolytic therapy in stroke include the following (Fitriyani et al., 2024):

### **Presence of intracranial hemorrhage**

Intracranial hemorrhage includes intraventricular hemorrhage, intraparenchymal hemorrhage, subarachnoid hemorrhage, epidural hematoma, subdural hematoma, and hemorrhagic transformation. The increased risk of bleeding-related adverse effects is thought to be associated with various individual patient factors, including time from symptom onset, disease etiology, definitive therapy that has already been performed, the presence of hematoma during surgical procedures, and the volume of encephalomalacia. Intracranial hemorrhage is an absolute contraindication to thrombolytic therapy because the associated risks clearly outweigh the potential benefits. A history of intracranial hemorrhage is likewise considered an absolute contraindication. However, the presence of cerebral microbleeds does not automatically constitute a contraindication to thrombolytic therapy; therefore, treatment decisions in such cases should be based on individual clinical considerations.

### **Symptoms suggestive of subarachnoid hemorrhage**

#### **Active internal bleeding**

#### **History of intracranial or intraspinal surgery or severe head trauma within the previous 3 months**

These conditions may increase the risk of bleeding. Thrombolytic administration in this population may result in adverse outcomes because patients with trauma may develop coagulopathy.

#### **Bleeding diathesis**

This includes a platelet count  $<100,000/\text{mm}^3$ , administration of heparin within the previous 24 hours accompanied by an increased aPTT, current use of anticoagulants with an INR  $>1.7$  or PT  $>15$  seconds, or current use of thrombin inhibitors or factor Xa inhibitors.

#### **Uncontrolled severe hypertension**

Uncontrolled hypertension, defined as a systolic blood pressure  $>185$  mmHg or a diastolic blood pressure  $>110$  mmHg, is associated with poor prognosis and an increased risk of hemorrhage.

#### **Intracranial neoplasm or aneurysm**

#### **Blood glucose concentration $<50$ mg/dL**

Blood glucose levels should be assessed before thrombolytic therapy is administered. This assessment is necessary to confirm the diagnosis because symptoms of hypoglycemia and severe hyperglycemia may mimic stroke. In addition, both hypo- and hyperglycemia may worsen cerebral ischemia.

#### **Head CT scan demonstrating multilobar infarction**

One relative contraindication to thrombolytic therapy is age >80 years. Available studies indicate that favorable outcomes are less frequent and mortality is higher among ischemic stroke patients older than 80 years who receive thrombolytic therapy. The decision to administer thrombolysis should nevertheless be based on the individual patient's clinical condition. Other relative contraindications include severe stroke progressing to coma, a history of major surgery, a history of arterial puncture, gastrointestinal or urinary tract bleeding, seizure at symptom onset, recent myocardial infarction, structural lesions of the central nervous system, and dementia (Fitriyani et al., 2024).

In Indonesia, a thrombolysis eligibility checklist has been developed by the Department of Neurology, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo National General Hospital. According to this checklist, thrombolysis may be performed when all inclusion criteria are positive and none of the exclusion criteria are present. The inclusion criteria for thrombolysis are as follows (Tangkudung et al., 2020):

- 1) Age >18 years.
- 2) Clinical diagnosis of ischemic stroke with neurological deficits.
- 3) Symptom onset <6 hours.
- 4) Head CT scan showing no hemorrhage or non-stroke lesions.

The exclusion criteria are as follows (Tangkudung et al., 2020):

- 1) No history of intracranial hemorrhage.
- 2) History of arteriovenous malformation or aneurysm.
- 3) History of neurosurgery.
- 4) Severe head injury.
- 5) History of severe stroke within the previous 3 months.
- 6) History of gastrointestinal or urinary tract bleeding within the previous 21 days.
- 7) History of major surgery or severe trauma, arterial puncture, or lumbar puncture within the previous 14 days.
- 8) Clinical symptoms suggestive of subarachnoid hemorrhage, rapidly improving symptoms, or minor neurological symptoms (NIHSS <5).
- 9) Systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg.
- 10) Acute bleeding or acute trauma.
- 11) Seizure at symptom onset.
- 12) Coma or severe impairment of consciousness.
- 13) In laboratory testing, patients with a history of anticoagulant use and an INR >1.5.
- 14) Patients receiving heparin or novel oral anticoagulants (NOACs) with increased aPTT, or a platelet count of 400 mg/dL.

### **Intra-Arterial Thrombolysis**

Before the development of modern mechanical thrombectomy, intra-arterial thrombolysis was the primary endovascular strategy for the management of acute ischemic stroke. This therapy involves the direct administration of thrombolytic agents, such as tissue plasminogen activator (tPA) or urokinase, into the blood clot through a catheter. In cases of *large vessel occlusion* (LVO), intra-arterial thrombolysis provides a higher recanalization rate, approximately 60–70%, compared with intravenous thrombolysis (IV tPA). However, this approach was eventually replaced by mechanical thrombectomy, which can remove blood clots more rapidly and effectively (Listyawan & Setyawan, 2025).

In addition to intravenous thrombolysis, intra-arterial thrombolysis was previously a primary strategy in the management of acute ischemic stroke before the era of modern mechanical thrombectomy. Thrombolytic agents such as tPA or urokinase are administered directly to the site of the thrombus through a catheter. Although this method provides higher recanalization rates than intravenous thrombolysis in cases of LVO, its use was subsequently

replaced by mechanical thrombectomy, which is considered faster and more effective (Listyawan & Setyawan, 2025).

Currently, intra-arterial thrombolysis is more commonly positioned as an adjunctive therapy during mechanical thrombectomy procedures. The rationale for this approach is that, although the primary occlusion has been successfully removed and reperfusion has been achieved to the level of *Thrombolysis in Cerebral Infarction* (TICI), distal emboli or microvascular thrombi may remain. These conditions may impair tissue perfusion and limit the patient's functional recovery (Listyawan & Setyawan, 2025).

Intra-arterial (IA) thrombolysis is most commonly performed in patients with middle cerebral artery occlusion, and evidence indicates that the therapeutic window for IA thrombolysis may extend to 6 hours after stroke onset in cases of MCA occlusion. Other potential candidates include patients with internal carotid artery occlusion, "T"-type *Internal Carotid Artery* (ICA) occlusion involving the proximal MCA and distal carotid artery, as well as basilar artery occlusion. The NIHSS (*National Institutes of Health Stroke Scale*) score may also be considered, with patients scoring above 10 potentially being candidates for IA thrombolysis (Utomo, 2022).

Initial patient evaluation includes basic laboratory examinations, consisting of a complete blood count, coagulation tests (TT, aPTT, INR, CT, fibrinogen, plasminogen),  $\alpha$ -antiplasmin, serum electrolytes, random blood glucose, troponin, creatine kinase, CK-MB, and electrocardiography (ECG). A head CT scan is performed to exclude hemorrhagic stroke. In approximately one-third of acute stroke cases caused by MCA occlusion, CT scans may demonstrate a hyperdense MCA sign, indicating the presence of a thrombus (Utomo, 2022).

Various catheter designs and techniques have been used in IA thrombolysis. In most cases, a single end-hole microcatheter is used, whereas a multiple end-hole microcatheter may be used for longer thrombi. Superselective angiography through the microcatheter is performed periodically to assess the degree of thrombus lysis and to adjust the dose and volume of the thrombolytic agent. If partial thrombus dissolution occurs, the catheter can be advanced into the remaining thrombus. As the thrombus dissolves, the catheter is directed more distally into the intracranial circulation so that most of the thrombolytic agent enters the occluded vessel. Recanalization may be achieved within 2 hours after the procedure begins, although successful recanalization is uncommon when partial recanalization of the vessel does not occur within the first hour. The primary objective of this procedure is to achieve recanalization as rapidly as possible while using the minimum amount of thrombolytic agent necessary to prevent cerebral infarction and reduce the risk of hemorrhage (Utomo, 2022).

Various agents have been used in stroke thrombolysis, including streptokinase, urokinase, alteplase, pro-urokinase, reteplase, tenecteplase, and desmoteplase. In principle, all of these agents act by converting the proenzyme plasminogen into plasmin, which subsequently cleaves fibrin into fibrin degradation products. The advantages of intra-arterial thrombolysis over intravenous thrombolysis include the ability to deliver the drug directly to the thrombus at a lower systemic dose, as well as requiring less instrumentation than mechanical techniques. In addition, chemical thrombolysis can act on distal clots, such as those located in the M2, M3, and smaller branches, which are difficult to reach using mechanical techniques (Utomo, 2022).

The indications for intra-arterial thrombolysis continue to evolve because there are no specific officially approved indications for stroke, resulting in considerable variation among practitioners. In general, IA thrombolysis may be considered in patients with Acute Ischemic Stroke (AIS) for up to at least 6 hours in cases of MCA occlusion and may be considered for even longer periods in vertebrobasilar circulation, where successful treatment has been

reported up to 48 hours after stroke onset. The longer therapeutic window for posterior circulation occlusion is thought to be associated with better collateral blood flow in this region (Utomo, 2022).

IA thrombolysis may also be beneficial in situations where intravenous thrombolysis carries a high risk of hemorrhage. Patients with recent surgery, non-ICH conditions, or arterial puncture, as well as patients with prior anticoagulant use, were excluded from studies conducted by the *National Institute of Neurological Disease and Stroke* (NINDS) because of their high risk of hemorrhage. In such situations, IA thrombolysis, using a smaller dose of thrombolytic agent delivered directly into the blood vessel, offers the potential for treatment with a lower risk of bleeding (Utomo, 2022).

### **Mechanical Thrombectomy**

Mechanical thrombectomy performed within 6 hours after stroke onset should be considered in all eligible patients, including those who have received fibrinolytic therapy. The *American Heart Association/American Stroke Association* (AHA/ASA) guidelines recommend proceeding with mechanical thrombectomy without waiting for a response to intravenous tPA administration in patients who meet the criteria for the procedure. In recent years, the management of acute stroke has undergone significant advances. Several clinical trials published in 2015 demonstrated that endovascular thrombectomy performed within the first 6 hours was substantially more beneficial than standard medical care in patients with *large vessel occlusion* (LVO) involving the proximal anterior circulation. The benefits of thrombectomy were consistently demonstrated across different geographic regions and diverse patient populations (Lui et al., 2025).

Mechanical thrombectomy may also be considered within a longer therapeutic window, namely 16 to 24 hours after stroke onset, with the assistance of perfusion imaging studies such as CT perfusion or MRI perfusion. These imaging modalities can identify areas of ischemic brain tissue that have not yet undergone permanent infarction, known as the ischemic penumbra. When the penumbra is relatively larger than the ischemic core, a substantial amount of brain tissue may remain salvageable through restoration of blood flow in cases of LVO identified by CT angiography or MRI, thereby resulting in better clinical outcomes (Lui et al., 2025).

In 2018, an important paradigm shift occurred in stroke care following the publication of the DAWN trial. This trial demonstrated significant benefits of endovascular thrombectomy in patients with LVO of the proximal anterior circulation by extending the treatment window to 24 hours in selected patients based on perfusion imaging. Consequently, more patients could potentially benefit from thrombectomy, even up to 24 hours after stroke onset. Based on these findings, mechanical thrombectomy is recommended within 6 to 16 hours from the time the patient was last known to be well in selected patients with acute ischemic stroke caused by LVO in the anterior circulation who meet the DAWN and DEFUSE 3 criteria. In selected patients meeting the DAWN criteria, mechanical thrombectomy may also remain appropriate up to 24 hours after the last known well time (Lui et al., 2025).

### **Thrombolytic Agents**

The history of thrombolytic therapy began in 1933, when it was discovered that filtrates from cultures of beta-hemolytic Group A *Streptococcus* were capable of dissolving blood clots, an agent that subsequently became known as streptokinase. In 1958, streptokinase was first used in patients with acute myocardial infarction and subsequently changed the therapeutic approach to this condition. Later, in 1947, a potential thrombolytic agent derived from human urine was described, and its active molecule was named urokinase. Unlike streptokinase, urokinase is non-antigenic and can directly activate plasminogen into plasmin. During the 1980s, tissue plasminogen activator (tPA) was

developed as a natural thrombolytic agent produced by vascular endothelial cells and involved in maintaining the balance between thrombolysis and thrombogenesis. At the site of a thrombus, the binding of tPA to plasminogen on the fibrin surface induces a conformational change that converts plasminogen into plasmin, thereby allowing the blood clot to dissolve (Rilianto, 2016).

Thrombolytic agents are generally divided into two categories: fibrin-specific agents and fibrin-nonspecific agents. Fibrin-specific agents include alteplase (tPA), reteplase (*recombinant plasminogen activator* [R-PA]), and tenecteplase. Meanwhile, fibrin-nonspecific agents include streptokinase, which is indicated for acute myocardial infarction, acute pulmonary embolism, deep vein thrombosis, and arterial thrombosis. However, the use of streptokinase as a thrombolytic agent has currently declined compared with tPA because streptokinase causes more extensive fibrinogenolysis (Rilianto, 2016).

In addition, several other intravenous thrombolytic agents, such as reteplase, urokinase, anistreplase, and staphylokinase, have not been extensively evaluated. Desmoteplase is a thrombolytic agent derived from bat saliva. Tenecteplase is a modified form of tPA with a longer half-life and greater fibrin specificity than alteplase. It has demonstrated promising potential, with better reperfusion capacity and a lower incidence of hemorrhagic complications (Rilianto, 2016).

### **Streptokinase**

Because of its relatively low cost and favorable efficacy and safety profile, streptokinase is one of the most widely used fibrinolytic agents worldwide. Although its efficacy is lower than that of alteplase, the risk of intracranial hemorrhage is lower. Re-administration of streptokinase within six months is not considered safe because of its high antigenicity and high titers of antistreptococcal antibodies. Streptokinase is not itself a plasminogen activator. However, after binding to freely circulating plasminogen, it forms a complex that converts additional plasminogen into active plasmin. Because it is produced by *Streptococcus*, streptokinase frequently causes febrile reactions and other allergic reactions. Dose-dependent hypotension is another potential warning associated with this drug (Baig & Bodle, 2023).

### **Alteplase**

Alteplase is a recombinant plasminogen activator that is identical to native tPA and is more specific for fibrin, with a plasma half-life of 46 minutes. It is the most frequently used fibrinolytic agent in the treatment of acute cardiovascular events, including ST-elevation myocardial infarction (STEMI), pulmonary embolism (PE), and acute ischemic stroke (AIS). Theoretically, alteplase should be active only on the surface of fibrin clots. However, it also produces systemic fibrinolysis; consequently, substantial amounts of circulating fibrin degradation products have been observed, with a moderate risk of bleeding. Alteplase is non-antigenic and is therefore rarely associated with allergic manifestations (Baig & Bodle, 2023).

### **Tenecteplase (TNK-tPA)**

Tenecteplase is a fibrinolytic agent commonly used in the United States, except for ischemic stroke, as well as in Canada and many European countries. Tenecteplase is as effective as alteplase but has a lower risk of non-cerebral bleeding. It has greater fibrin specificity and a longer plasma half-life, with terminal clearance occurring primarily through hepatic metabolism. In addition, tenecteplase is non-antigenic and more convenient to administer (Baig & Bodle, 2023).

### **Reteplase**

Reteplase is a second-generation recombinant plasminogen activator that acts more rapidly and has a lower tendency to cause bleeding than the first-generation agent alteplase. Reteplase exhibits weaker binding to fibrin than native tPA, allowing greater free diffusion

through the blood clot rather than binding only to the clot surface as tPA does. In addition, reteplase does not exhibit competitive inhibition of plasminogen, thereby allowing plasminogen to be converted into plasmin, which dissolves the blood clot. Collectively, these characteristics explain its faster clot resolution compared with other agents. The FDA approved reteplase as two 10-U boluses administered 30 minutes apart for the treatment of AMI. Each bolus is administered over two minutes. Similar to alteplase, reteplase may be readministered when necessary and is non-antigenic (Baig & Bodle, 2023).

### **Urokinase**

Urokinase is most commonly used for occluded catheters and peripheral vascular thrombi. It is considered a physiological thrombolytic agent that is normally produced by the renal parenchyma and is therefore purified from human urine. Recombinant urokinase is also commercially available. Unlike streptokinase, urokinase directly cleaves plasminogen into plasmin. Its low antigenicity allows repeated administration without antigenic complications (Baig & Bodle, 2023).

### **Prourokinase**

Prourokinase is a relatively inactive precursor that requires conversion into urokinase to become active. This requirement for conversion provides pro-urokinase with fibrin-specific physiological properties. It is a newer agent that has undergone clinical trials (Baig & Bodle, 2023).

### **Anistreplase**

Anisoylated plasminogen–streptokinase activator complex (APSAC), or anistreplase, is a complex of streptokinase and plasminogen that does not depend on circulating plasminogen to exert its effect. Although it offers several theoretical advantages over streptokinase, it has high antigenicity. Upon administration, the acyl group is spontaneously hydrolyzed, releasing the activated streptokinase–proactivator complex. Similar to streptokinase, anistreplase does not distinguish between circulating plasminogen and fibrin-bound plasminogen; consequently, it produces a state of systemic lysis (Baig & Bodle, 2023).

### **Imaging Before Thrombolysis**

Brain imaging to exclude intracerebral hemorrhage (ICH) is a primary requirement before the administration of intravenous alteplase in patients with acute ischemic stroke. CT scans are more commonly selected because they are rapid and widely available. In cases of diagnostic uncertainty, hyperacute changes associated with infarction may help strengthen the clinical suspicion. One important advancement in CT evaluation is the use of the *Alberta Stroke Program Early CT Score* (ASPECTS), an objective method for assessing early ischemic changes on initial CT scans, which also has prognostic value. An ASPECTS greater than 7 has been associated with reduced mortality and greater benefit in patients receiving thrombolysis (Robinson et al., 2011).

MRI has potential advantages over CT because, in addition to excluding ICH using gradient-echo echo-planar imaging (EPI) sequences, MRI can identify acute infarction within approximately 30 minutes of stroke onset through *diffusion-weighted imaging*. This is particularly useful in situations involving clinical uncertainty. Furthermore, MRI can help identify patients at high risk of ICH by detecting extensive cerebral infarction. Nevertheless, the use of MRI is limited by equipment availability and longer scanning times. MRI also has a potential role in patients who awaken with stroke symptoms, given that approximately 25% of stroke events occur while patients are asleep. Patients in this group are generally excluded from thrombolysis because the time of symptom onset is uncertain. By identifying potentially salvageable brain tissue, MRI may assist in selecting patients who are potentially likely to benefit from thrombolysis (Robinson et al., 2011).

## **Ultrasonography and Thrombolysis**

Transcranial Doppler (TCD) ultrasonography can be used in combination with rt-PA to increase the rate of reperfusion in acute ischemic stroke (AIS). TCD is also useful for detecting and localizing arterial occlusions and monitoring the reperfusion process. Ultrasonography works by applying mechanical forces at the interface between stagnant blood flow and the blood clot. The resulting mechanical agitation may expose the outer layers of the thrombus to circulating rt-PA and ultimately enhance the fibrinolytic process (Robinson et al., 2011).

Ultrasonography can be classified according to frequency into low-frequency and high-frequency modalities. Low-frequency ultrasonography produces greater mechanical forces and is more effective in enhancing the effects of rt-PA; however, its use is associated with a substantially higher risk of intracranial hemorrhage (ICH) and it cannot be used for vascular imaging, thereby limiting its clinical utility. In contrast, high-frequency ultrasonography in the range of 1.0–2.2 MHz includes TCD, transcranial color Doppler, and the use of microspheres (Robinson et al., 2011).

## **Hemorrhagic Complications**

Thrombolytic therapy has good efficacy and effectiveness in the management of acute ischemic stroke; however, it also carries a risk of potentially fatal complications, particularly hemorrhage. Intracranial hemorrhage was reported in 6.4% of patients in the NINDS trial and ranged from 2–7% in the ECASS III study. Several studies have indicated that Asian populations have a slightly higher proportion of intracranial hemorrhage than Western populations. Intracranial hemorrhage is generally suspected in patients who experience rapid neurological deterioration following tPA administration, usually within the first 24 hours, characterized by a decrease in the NIHSS score of more than 4 points and a reduction in the GCS (*Glasgow Coma Scale*) score. Systemic bleeding may also occur, although it is generally not life-threatening (Rilianto, 2022).

Several factors are known to contribute to an increased risk of post-thrombolysis hemorrhage, including older age, severe stroke, the presence of early ischemic signs on CT scans, high initial blood glucose levels, and delayed administration of tPA after symptom onset. The major complication of thrombolytic therapy is bleeding, with intracranial hemorrhage reported in approximately 7%–8% of patients. Patients with severe stroke are indeed at greater risk of hemorrhage; however, to date, there is no evidence that this group does not benefit from intravenous thrombolytic therapy (Rilianto, 2022).

In older patients, the risk of intracranial hemorrhage has not been demonstrated to increase, although clinical outcomes tend to be poorer and mortality is higher. In addition to age and NIHSS score, other risk factors for intracranial hemorrhage include hypodensity on CT scans, elevated blood glucose levels, and persistent proximal arterial occlusion 2 hours after intravenous tPA administration. Systemic bleeding has been reported in approximately 0.4%–1.5% of patients. Management of post-thrombolysis intracranial and systemic hemorrhage is generally recommended with cryoprecipitate and platelet administration, although the scientific evidence supporting this approach remains limited (Rilianto, 2022).

In addition to hemorrhage, other complications of thrombolytic therapy include facial angioedema, which has been reported in approximately 1%–5% of patients. In most cases, the symptoms of angioedema are mild and resolve rapidly; however, the condition can become dangerous if it causes airway obstruction. Management includes the administration of glucocorticoids and antihistamines. Other adverse effects that may occur with all fibrinolytic agents include hypotension, allergic reactions, anaphylactic shock, and reperfusion arrhythmias, particularly when these agents are used in acute myocardial infarction (Rilianto, 2022).

Among all fibrinolytic agents, streptokinase is the most antigenic and therefore most frequently causes complications such as allergic reactions and hypotension. Bleeding may occur either at the puncture site or spontaneously at various sites throughout the body, with intracranial hemorrhage or hemorrhagic stroke being the most feared complications. Risk factors for bleeding include advanced age, uncontrolled hypertension, a history of stroke or recent surgery, bleeding diathesis, and concomitant anticoagulant use. Thrombolytic overdose, which may occur when the dose is not adjusted according to body weight, can result in severe hemorrhagic complications. In addition, cholesterol embolism has been reported in patients receiving thrombolytic therapy and may cause blue toe syndrome or “purple toe” as well as acute kidney injury (Baig & Bodle, 2023).

### **Monitoring**

Patients receiving thrombolytic therapy should undergo continuous neurological and cardiovascular evaluation. Blood pressure should be monitored every 15 minutes during and after the tPA infusion for at least 2 hours, followed by every 30 minutes for 6 hours and then every hour for the subsequent 16 hours after injection. Close blood pressure monitoring is essential to prevent complications. Thrombolytic therapy should be discontinued immediately if signs of neurological deterioration develop, and the patient should promptly undergo emergency computed tomography (CT) examination. Cardiac monitoring is also necessary because of the risk of reperfusion arrhythmias.

The physician should also obtain the *National Institutes of Health Stroke Scale* (NIHSS) score to assess stroke severity and determine whether the patient is a potential candidate for fibrinolytic therapy. If evidence of hemorrhagic complications develops in a patient undergoing fibrinolytic therapy, fibrinolytic agents or anticoagulants should be discontinued immediately. Subsequent management is supportive, including volume correction and blood factor transfusion. In patients receiving concomitant heparin therapy, the effects of heparin can be reversed through the administration of protamine sulfate (Baig & Bodle, 2023).

## **CONCLUSION**

Acute ischemic stroke is a neurological emergency that requires rapid and appropriate management to minimize brain tissue damage and reduce disability and mortality rates. One of the fundamental principles in the management of acute ischemic stroke is early reperfusion to restore blood flow to ischemic areas of the brain, particularly the penumbra, which consists of tissue that remains potentially salvageable.

Thrombolytic therapy plays an important role as a reperfusion modality in acute ischemic stroke. The administration of thrombolytic agents, either intravenously or intra-arterially, aims to lyse the thrombus responsible for cerebral vascular occlusion and improve the patient's functional status. The success of thrombolytic therapy depends considerably on appropriate patient selection, administration within the appropriate therapeutic window, and adequate clinical and imaging evaluation.

Although thrombolysis provides significant benefits, it also carries risks, particularly intracranial hemorrhage; therefore, its implementation must be performed cautiously and in accordance with applicable guidelines. Consequently, a comprehensive understanding of the indications, contraindications, mechanisms of action, and complications of thrombolytic therapy is essential for medical professionals in the management of patients with acute ischemic stroke.

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