WJPMR, 2026, 12(2), 187-195

Review Article

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Impact Factor: 6.842

ISSN (O): 2455-3301

ISSN (P): 3051-2557

Coden USA: WJPMBB

INTRACRANIAL HEMORRHAGE RISK ASSOCIATED WITH THROMBOLYTIC THERAPY IN ISCHEMIC STROKE: A REVIEW

K. R. Sathya Ramanan[1]*, S. Satheesh[2]

[*1]Pharm D. Intern, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, Namakkal District, Tamilnadu-638183, India, 0009-0009-1175-6560.

[2]Associate Professor, Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, Namakkal District, Tamilnadu-638183, India, 0000-0001-7179-1143.

***Corresponding Author: K. R. Sathya Ramanan**

Pharm D. Intern, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, Namakkal District, Tamilnadu-638183, India, 0009-0009-1175-6560.

DOI: https://doi.org/10.5281/zenodo.18429763

How to cite this Article: K. R. Sathya Ramanan[1]*, S. Satheesh[2]. (2026). Intracranial Hemorrhage Risk Associated With Thrombolytic Therapy In Ischemic Stroke: A Review. World Journal of Pharmaceutical and Medical Research, 12(2), 187–195.

Article Received on 30/12/2025 **Article Revised on 20/01/2026** **Article Published on 01/02/2026**

ABSTRACT

Ischemic stroke is a medical emergency caused by disrupted blood flow to the brain, leading to brain cell death. Thrombolytic agents like alteplase have been effective in treating acute ischemic stroke by breaking down blood clots. However, this treatment also poses the risk of intracranial hemorrhage (ICH). This review examines the incidence, risk factors, and management of ICH associated with thrombolytic therapy in ischemic stroke. The review discusses key clinical trials and meta-analyses that assess the risk of ICH with thrombolytic therapy. Scoring systems, such as the ICH Score and Essen ICH Score, are highlighted as tools for predicting ICH risk based on patient characteristics. Management and prevention strategies for ICH in thrombolytic therapy are explored, including careful blood pressure control, reversal of anticoagulation, and other interventions to reduce bleeding risk. Novel approaches involving neuroprotective agents like minocycline are also discussed as potential interventions to reduce secondary injury mechanisms after ICH. The review emphasizes the importance of individualized decision-making when considering thrombolytic therapy, weighing potential benefits against the risk of ICH for each patient. Clinical guidelines are outlined to aid clinicians in making informed treatment decisions. Overall, this review underscores the need for ongoing research to optimize patient selection and treatment strategies, with the ultimate goal of reducing complications and improving outcomes in ischemic stroke patients at risk of ICH associated with thrombolytic therapy.

KEYWORDS: Acute Ischemic Stroke, Alteplase (tPA), Intracranial Hemorrhage, (ICH), Neuroprotective Agents, Predictive Scoring System Thrombolytic Therapy.

1. INTRODUCTION

A stroke is a medical emergency that happens when blood flow to the brain is disrupted or obstructed. This could result from a blood clot blocking a blood artery in the brain (ischemic stroke) or a blood vessel in the brain rupturing (hemorrhagic stroke). When this occurs, the brain cells are starved of oxygen and nutrition, which means they commence to die within minutes.[1] Ischemic stroke is the most common type of stroke, accounting for about 87% of all strokes, It occurs when a blood clot blocks blood flow to the brain.[2] When thrombolytic treatment is used to treat an acute ischemic stroke, intracranial hemorrhage (ICH) is a significant side effect. Blood clots that result in an ischemic stroke can be broken up by thrombolytic medications. However, using these drugs might make you more likely to develop ICH.[3-6] ICH has been reported in 1.7% to 8.8% of patients with acute ischemic stroke treated with iv thrombolysis, mortality and morbidity rates increase in patients with symptomatic ICH. And studies also states blacks have higher rates of both ischemic and hemorrhagic stroke compared with whites. They are also at higher risk for intracranial hemorrhage after thrombolysis.[7-10]

Thrombolytic medicines are the most effective pharmacological treatment for acute ischemic stroke (AIS) in terms of increasing survival and decreasing morbidity.[11,12] If administered within three hours of the onset of the first stroke symptoms, it is able to rapidly break down the clot and reduce stroke damage and disabilities.[13] The only FDA approved remedy for acute ischemic stroke is thrombolytic therapy utilizing alteplase, also known as "tissue plasminogen activator (tPA)," as it has been shown to improve patient outcomes after a stroke.[14] Clinical investigations have reported a 50% risk of cerebral haemorrhage related to thrombolytic treatment. Although the real risk varies from 2% to 7% depending on the patient's profile and the kind of intracerebral hemorrhage, it is dependent on both.[15] However thrombolytic treatments can potentially result in intracranial hemorrhage (ICH). The fact that ICH almost always develops in the centre of the infarction raises the possibility that ischemia itself is involved. A few susceptibility indicators for functional ICH (SICH) have been identified, including leukoaraiosis, prior use of stains or anti-platelet medications, prior micro-bleeds on brain MRIs, and other variables. Matrix metalloproteinases in the serum have become a viable diagnostic for improved patient selection.[16]

Therefore, this review includes the thrombolytic therapy related to risk associated with intracranial hemorrhage in ischemic stroke, In this review article, we will discuss the incidence, risk factors, and management of ICH associated with thrombolytic therapy for acute ischemic stroke. We will also discuss the current state of knowledge regarding the pathophysiology of ICH and the potential role of new therapeutic strategies in reducing its incidence.

2. OVERVIEW OF THROMBOLYTIC AGENTS IN ISCHEMIC STROKE TREATMENT

In order to address clot formation, thrombolytic drugs are a life-saving medication. Thrombolytic drugs work by transforming plasminogen into plasmin, an enzyme that dissolves fibrin clots. The tissue plasminogen activator (tPA), used to treat ischemic stroke, converts plasminogen to plasmin.

Alteplase: The only thrombolytic drug that the FDA has approved for application during acute ischemic stroke is called alteplase. It is a recombinant tissue-type plasminogen activator (tPA) that cleaves fibrin-bound plasminogen to plasmin to degrade fibrin in clots. It needs to be administered by bolus and infusion because its half-life is only 4-5 minutes. There is a higher chance of serious bleeding and cerebral haemorrhage as a result.

Tenecteplase: This protein was produced as a result of alteplase mutagen studies. Its thrombolytic efficacy is ten times higher than alteplase, its clearance is six to eight times slower, and its resistance to PAI-1 is eighty times higher. It takes two minutes to prepare and deliver and can be administered as a single intravenous bolus over five seconds. In individuals with big vascular blockage, it may be preferable than alteplase and has a similar safety and effectiveness profile in AIS.

Desmoteplase: This is a highly fibrin-specific thrombolytic enzyme that was isolated from vampire bat saliva. Desmoteplase was explored for an extended window of AIS therapy (3–9 hours following the start of symptoms), however, it did not show any difference in neurological results at 90 days compared to placebo in patients.

Reteplase: Another recombinant thrombolytic drug with an extended half-life than alteplase, developed from natural tPA, targets fibrin. It was evaluated in AIS using both intravenous and intraarterial methods, but it failed to outperform alteplase in terms of functional result or recanalization.

Streptokinase: A very specialised 1:1 enzymatic complex is formed with plasminogen by thrombolytic medicine that activates plasminogen via the nonenzymatic method, turning dormant plasminogen-stimulating molecules into active plasmin. Fibrin clots, fibrinogen, and various other plasma proteins are all broken down by plasmin. Blood clots then degrade as a result of this.

Urokinase: A serine protease enzyme called urokinase converts plasminogen into an active fibrinolytic protease. It breaks down plasminogen to produce plasmin, an active fibrinolytic protease. Fibrin clots, fibrinogen, and various other plasma proteins are all broken down by plasmin. Blood clots then degrade as a result of this.[17-20]

3. INTRACRANIAL HEMORRHAGE: CLASSIFICATION AND PATHOPHYSIOLOGY

Table 1: Overview of ICH class and its concers.

SI.NO	ICH CLASS AND ITS CONCERNS
1	Primary ICH: This sort of bleeding occurs inside the brain parenchyma and is not related to coagulopathy, tumours, vascular abnormalities, or trauma. Around 80 percent of ICH events are a result of this condition, which is typically brought on by elevated blood pressure, amyloid angiopathy, or cerebral venous thrombosis.
2	Secondary ICH: This sort of bleeding occurs inside the brain parenchyma and is brought on by a variety of underlying medical conditions, including tumours, coagulopathies, vascular abnormalities, and trauma. It has a less favourable outcome than primary ICH and makes up around 20% of all ICH patients.
3	Subarachnoid hemorrhage (SAH): The subarachnoid area, which encircles the brain and spinal

	cord, is bleeding as a result. Arteriovenous malformations or aneurysm rupture are the typical culprits. It may result in a terrible headache, stiff neck, photophobia, and unconsciousness.
4	Epidural hematoma (EDH): This haemorrhaging occurs associated with the dura mater, the meninges' outer covering, and the skull. Typically, a skull fracture and middle meningeal artery rupture are the result of trauma. It can result in a brief period of lucidity followed by a sharp decline in neurological function.
5	Subdural hematoma (SDH): This is bleeding in the meningeal intermediate layer, dura mater and the mater of the arachnoid. The blood vessels that run across the dura mater and the brain are typically torn after trauma, which is the common cause. According to the rate of bleeding, it might result in either chronic or acute symptoms.

The common Pathophysiological mechanisms leading to intracranial hemorrhage (ICH) are complex and depend on the underlying cause of the bleeding: *Hypertension*: Chronic hypertension can cause small vessel disease and lead to microbleeds and lacunar infarcts that can eventually progress to ICH. *Cerebral amyloid angiopathy (CAA)*: In this kind of condition, amyloid protein builds up in the linings of the cerebral blood vessels, which renders them brittle and prone to rupture. *Coagulopathy*: This is an illness where the blood's capacity to coagulate is compromised for a number of reasons, including the use of anticoagulants, liver illness, or a lack of vitamin K. *Trauma*: This is a frequent reason for ICH and can be brought on by a penetrating or traumatic head injury. *Vascular malformations*: These are kinds of aberrant blood vessels that might exist from birth or form later in life. They consist of dural arteriovenous fistulas (DAVFs), cavernous malformations, and arteriovenous malformations (AVMs). *Tumors*: These can cause ICH by eroding blood vessels or by causing abnormal angiogenesis.[21]

Intracerebral hemorrhage (ICH) and acute ischemic stroke (AIS) have common vascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, and obesity1. However, the reason for the onset of different subtypes, ICH or AIS, is unclear.[22] Hypertension, current smoking, excessive alcohol intake, hypocholesterolemia, and drug use are risk factors for ICH. The othger risk factors for ICH include advanced age, male gender, Asian ancestry, cerebral microbleeds (CMBs), chronic renal disease and the development of cerebral amyloid angiopathy (CAA).[23]

4. CLINICAL TRIALS AND META-ANALYSES EVALUATING ICH RISK

Several key clinical trials that have assessed the risk of intracranial hemorrhage (ICH) associated with thrombolytic therapy, including the Thrombolysis in Myocardial Infarction (TIMI) Study, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial, and the Individual Risk Assessment for Intracranial Hemorrhage During Thrombolytic Therapy (IRIS) study. The TIMI Study was a randomized, double-blind, placebo-controlled trial that examined the effectiveness and reliability of tissue plasminogen activators (tPA) for patients with acute myocardial infarction (AMI). According to the study, tPA enhanced clinical outcomes and diminished mortality in patients with AMI, but it was also linked to a higher risk of ICH. The GUSTO-1 trial was a large, international, randomized trial that compared the the effectiveness and safety of streptokinase and tPA in patients with AMI. The experiment demonstrated that while tPA was linked with a greater possibility of ICH than streptokinase, but was additionally associated with a more substantial decline in death rates. The IRIS research was a retrospective cohort study that analyzed information from medical records to calculate the risk and find predictors of ICH linked to thrombolytic treatment. The study found that the rate of ICH was 1.43% among Medicare-covered patients who have been discharged with the principal diagnosis of AMI who were administered with thrombolytic therapy. The study also identified several predictors of ICH, including older age, female sex, and a history of stroke or hypertension.[24]

1. *The PROACT II trial*: In this study, individuals with acute ischemic stroke were assessed for their safety and response to intra-arterial thrombolysis using recombinant prourokinase. The trial discovered that the treatment group had a greater incidence of symptomatic cerebral bleeding than the placebo group (10% vs. 2%, p=0.04).
2. *The ECASS II trial*: This trial assessed the effectiveness and safety of the alteplase with other intravenous thrombolysis in individuals with acute ischemic stroke. Based to the study, there were more symptomatic cerebral hemorrhages in the treatment group (7.7% vs. 1.1%, p0.001) than in the placebo group.
3. *The Multicenter rt-PA Stroke Survey*: The study evaluated the outcomes and efficacy of the alteplase with intravenous thrombolysis in clinical settings. The study discovered that symptomatic cerebral bleeding occurred 6.4% of the time and identified a number of risk variables for hemorrhagic complications, including advanced age, higher baseline blood glucose, and lower baseline platelet count.
4. *The Canadian Alteplase for Stroke Effectiveness Study*: In this experiment, the effectiveness and safety of IV thrombolysis with the alteplase in standard clinical practice were examined. In that the Incidence of symptomatic cerebral hemorrhage was determined to be 3.9% in the study, and many risk variables for hemorrhagic complications were also

discovered, including advanced age, higher baseline blood glucose, and lower baseline platelet count.

5. *The ECASS I trial*: In this study, individuals with acute ischemic stroke were evaluated to determine the effectiveness and safety of thrombolysis via IV with alteplase. The experiment showed that the treatment group had a greater rate of symptomatic cerebral bleeding than the placebo group (6.4% vs. 0.6%, p=0.008). Overall, these studies show that intracranial hemorrhage, especially symptomatic bleeding, is related with thrombolytic treatment for acute ischemic stroke and is associated with an elevated risk of intracranial hemorrhage. However, the advantages of thrombolytic treatment in terms of improved functional outcomes and reduced disability outweigh the risks in many cases.[25-27]

5. PREDICTIVE MODELS AND SCORING SYSTEMS FOR ICH RISK

Table 2: Scoring systems to estimate ICH risk in ischemic stroke patients.[28-31]

Scoring System	Factors Considered	Scoring	Purpose	Scoring assesment
ICH Score	Age, Glasgow Coma Scale score, ICH volume, Intraventricular hemorrhage presence, infratentorial etiology of ICH	0-6 points (higher score indicates higher risk)	Predicts 30-day mortality rate of ICH patient	One point is given for each of the following: age >80 years, Glasgow Coma Scale score of 3-4, ICH volume >30 mL, Intraventricular hemorrhage presence, infratentorial etiology of ICH.
Essen ICH Score	Age, Glasgow Coma Scale score, ICH volume, Intraventricular hemorrhage presence, location of hematoma	0-9 points (higher score indicates higher risk)	Predicts 30-day mortality rate of ICH patient	Points are given based on the following criteria: age (0 points for <60 years, 1 point for 60-69 years, 2 points for 70-79 years, and 3 points for ≥80 years), Glasgow Coma Scale score (0 points for 15, 1 point for 13-14, 2 points for 9-12, and 3 points for ≤8), ICH volume (0 points for <15 mL, 1 point for 15-29 mL, and 2 points for ≥30 mL), presence of intraventricular hemorrhage (2 points), and location of hematoma (0 points for lobar and 1 point for non-lobar).
FUNC Score	Age, pre-stroke modified Rankin Scale score, National Institutes of Health Stroke Scale score	0-9 points (higher score indicates better functional outcome)	Predicts functional achieve of a patient with ICH	Points are given based on the following criteria: age (0 points for <60 years and 1 point for ≥60 years), pre-stroke modified Ranking Scale score (0 points for 0-2 and 1 point for ≥3), and National Institutes of Health Stroke Scale score (0 points for ≤10 and 1 point for each additional point above 10).

GLASGOW COMA SCALE

Component	Response	Score
Eye Opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Verbal Response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Motor Response	Obeys commands	6
	Localizes to pain	5
	Withdraws from pain	4
	Flexion to pain (decorticate)	3
	Extension to pain (decerebrate)	2
	None	1

The development and validation of predictive models for ICH risk involves several key steps and considerations. These models are typically developed using data from clinical studies or patient populations, and they use statistical methods such as multivariable logistic regression to identify the most important predictors of ICH risk.[32]

6. MANAGEMENT AND PREVENTION OF ICH IN THROMBOLYTIC THERAPY

Immediate care methods for intracerebral hemorrhage (ICH) in ischemic stroke patients include avoiding hemorrhage expansion, monitoring for and treating high levels of intracranial pressure, and managing other complications such as seizures and hydrocephalus.[33] Emergency department (ED) intracranial pressure (ICP) management strategies for intracerebral hemorrhage (ICH) patients include bed elevation on the head side between 30 and 45° with the head kept midline, appropriate analgesia and sedation, normocapneic ventilation or hyperventilation if herniating, and hypertonic solutions.[34]

In the acute phase of ICH care, strategies aimed at minimizing ongoing bleeding include reversal of anticoagulation and modest blood pressure depletion. In addition, numerous organizations advise the monitoring and control of glucose levels, temperature, and even, in some circumstances, intracranial pressure. Clinical studies are now being conducted to evaluate aggressive blood pressure control, hemostatic treatment, platelet transfusion, intraventricular thrombolysis and stereotactic hematoma evacuation.In the final foremost, avoiding a recurrence of ICH is crucial, and strict blood pressure surveillance is crucial.[35]

Strategies to minimize ICH risk during thrombolytic therapy: A keen eye must be paid to the pre-therapeutic glycaemia value and a complete protocol for managing the effects of increased blood pressure is required during the first 24 hours.[36] Approaches to reduce risk, including weight-adjusted dosages and catheter-directed treatment, should be taken into consideration for patients who are thought to be at high risk of significant bleeding. Additional study related to the acute pulmonary embolism situation is required to confirm risk variables and treatments to reduce severe bleeding.[37] The high 1-month case-fatality rate of approximately 40% and poor long-term outcome make it a major contributor to global morbidity and mortality. There are several interventions that can be used to lower the risk of ICH. Some of these include blood pressure control, smoking cessation, and limiting alcohol intake.[38]

7. NOVEL APPROACHES AND INTERVENTIONS FOR REDUCING ICH RISK

Surgeries are good source for ICH risk reducing intervention notably hematoma evacuation, which involves the removal of the hematoma through a craniotomy or minimally invasive techniques. Other surgical interventions include ventricular drainage, which involves the placement of a catheter into the ventricles to drain cerebrospinal fluid and reduce intracranial pressure.

One potential avenue for the treatment of ICH is the use of novel drugs to target secondary injury mechanisms. These mechanisms include the inflammatory cascade, perihematomal edema reduction, and hemoglobin degradation products-mediated toxicity. The inflammatory cascade is activated by the complement cascade and the formation of membrane attack complex, which can directly injure neuronal cells and indirectly enhance the inflammatory cascade, leading to the destruction of erythrocytes and the release of toxic heme byproducts, particularly iron. Perihematomal edema (PHE) is also a significant factor in neurologic injury after ICH, and its formation is a dynamic process that almost unequivocally undergoes enlargement, which occurs at a faster pace in the first few days but continues for weeks after ICH. Hemoglobin degradation products-mediated toxicity is another secondary injury mechanism that contributes to neurologic injury in ICH. Neuroprotective agents: minocycline, have shown promise in preclinical studies and may be effective in limiting secondary injury mechanisms after ICH.[39]

According to several clinical investigations, minocycline has been shown to decrease cerebral edema triggered by cerebral bleeding, enhance hematoma absorption, and minimize the time needed for hematoma absorption. Clinical studies have also been undertaken to establish the safety of the medication. Additionally, it has been discovered that it can lessen subsequent cerebral edema and decrease neuroinflammation along with reducing iron overload post intracerebral haemorrhage.[40,41]

In similar studies conducted from 2013 to 2016, safety profiles, the pharmacokinetic and anti-inflammatory of minocycline were assessed in following events of intracerebral hemorrhage. A single-site, randomized, controlled trial of the drug minocycline was conducted. The study discovered that while oral treatment of minocycline in these critically sick individuals resulted in delayed absorption, it was safe and attained neuroprotective serum concentrations.[42]

8. INDIVIDUALIZED DECISION-MAKING AND CLINICAL GUIDELINES

Thrombolysis has been shown to improve outcomes in eligible patients, it also carries a risk of ICH, This reflects still the most dreaded side effect of thrombolysis for stroke. The possibilty of ICH risk is higher in patients with certain clinical and radiological features. The benefits of thrombolytic therapy are greatest when treatment is initiated early, within the first few hours of symptoms emerged. The risks of thrombolytic therapy can be minimized by careful patient selection, including consideration of age, stroke severity, and other possible risk factors for hemorrhagic complications. Overall, the

decision to use thrombolytic therapy in ischemic stroke patients should be based on a careful assessment of the potential benefits and risks for each individual patient in recommended time window.[43,44]

ICH is a severe side effect of thrombolytic treatment, which is used to treat stroke victims. The primary danger of thrombolytic treatment is internal bleeding, which affects 5% of patients with large bleeds and 1% of patients with brain bleeds that result in strokes.[45] There is an ongoing research into the risk factors for thrombolysis-related ICH. A systematic review and meta-analysis found that aging, elevated blood pressure, diabetes, atrial fibrillation, total cholesterol level, proteinuria, creatinine, fibrinogen levels, homocysteine, early infarct symptoms, antiplatelet medication, and anticoagulant therapy were all correlated with a higher risk of ICH.[46]

Prophylaxis measures can be mainly categorized into mechanical prophylaxis and chemoprophylaxis. Early mechanical prophylaxis, especially with intermittent pneumatic compression, is recommended by recent guidelines in regard to patients with sudden ICH. Since anticoagulants can raise the risk of recurrent ICH and hemorrhage growth, physicians disagree on the ideal course of treatment for chemoprophylaxis and anticoagulation medication. Regarding the best anticoagulants, when to start using them, and how much to take, there are still concerns. According to the available data, it is thought that beginning chemoprophylaxis with the use of unfractionated heparin (UFH) along with low molecular weight heparins (LMWH) within 24 to 48 hours of the onset of ICH in stroke may be safe; And on otherhand anticoagulation therapy should be based on each patient's specific clinical condition; and NOACs may have a promising role in this patient population.[47]

Studies comparing UFH and LMWH generally show that LMWH is more effective and causes less bleeding. However, certain circumstances still call for UFH on (GFR 30 ml/min) Renal failure. And need to rapidly stop anticoagulation.[48,49]

The guidelines From the American Heart Association/American Stroke Association also emphasize the importance of identifying markers of both microvascular and macrovascular hemorrhage pathogeneses. Hematoma growth is associated with a deprived ICH future outcomes, and there are currently several of neuroimaging indicators that might assist detect the risk of hematoma development. Further Approaches to therapy that restrict blood pressure fluctuation and achieve smooth, sustained blood pressure management after mild to moderate ICH happen to lessen hematoma development and produce better functional results.[50]

Future directions in optimizing patient selection and treatment strategies in intracranial hemorrhage (ICH) in stroke patients may include the refinement of currently available technology and addressing current limitations of established techniques. The ultimate goal of the evolution is to reduce complications and morbidity.[51] There have been no conclusively validated medicinal therapies for acute ICH in primary outcome assessments of randomized clinical studies. Surgery is usually recommended for ICH patients, however there is ongoing debate about the functions of different surgical techniques and the time that surgery needs to be undertaken.[52] Fast, accurate diagnosis of stroke is vital for selection of appropriate acute stroke treatment, such as intravenous tissue plasminogen activator (IV tPA) or endovascular mechanical thrombectomy treatment in ICH risk patient with stroke.[53]

9. RESULTS

The clinical analysis of thrombolytic therapy in acute ischemic stroke indicates that while agents like alteplase significantly improve functional outcomes, they are associated with a symptomatic intracranial hemorrhage (ICH) incidence ranging from 1.7% to 8.8%. High-scale clinical trials such as ECASS II and PROACT II confirmed a significantly higher risk of symptomatic bleeding in treated patients (7.7% and 10% respectively) compared to placebo groups. Key risk factors identified across studies include advanced age, female sex, Asian or Black ancestry, elevated baseline blood glucose, and pre-existing conditions like cerebral amyloid angiopathy (CAA). To mitigate these risks, scoring systems such as the ICH and Essen ICH scores are utilized to predict mortality, while management strategies focus on strict blood pressure control, anticoagulation reversal, and the investigation of neuroprotective agents like minocycline to reduce secondary injury.

10. DISCUSSION

The clinical application of thrombolytic therapy represents a critical balance between the high efficacy of agents like alteplase in breaking down clots and the "most dreaded" complication of intracranial hemorrhage (ICH). Pathophysiological evidence suggests that ICH often occurs within the infarct center, indicating that ischemia itself plays a significant role in vascular vulnerability. Risk stratification through tools like the ICH and Essen ICH scores is essential for individualized decision-making, especially when considering variables such as age, stroke severity, and biomarkers like serum matrix metalloproteinases. Management shifts from acute interventions—such as strict blood pressure control, head-of-bed elevation, and anticoagulation reversal—to the exploration of neuroprotective strategies. Specifically, the use of minocycline shows promise in reducing secondary injury by targeting the inflammatory cascade, perihematomal edema, and iron-mediated toxicity. Ultimately, while thrombolysis significantly improves functional outcomes, optimizing patient selection through clinical guidelines and

emerging therapeutic adjuncts remains vital to minimizing hemorrhagic risks and improving global recovery rates.

11. CONCLUSION

In conclusion, Thrombolytic agent, alteplase have shown effectiveness in improving outcomes in acute ischemic stroke by rapidly breaking down blood clots. However, they also increase the likelihood of ICH. Various clinical trials and meta-analyses have reported the incidence and risks of ICH associated with thrombolytic therapy, highlighting the importance of patient selection and risk assessment. Scoring systems, such as the ICH Score and Essen ICH Score, have been developed to predict ICH risk based on factors like age, Glasgow Coma Scale score, and ICH volume. Management and prevention strategies for ICH in thrombolytic therapy involve careful monitoring and control of blood pressure, reversal of anticoagulation, and addressing complications such as increased intracranial pressure. Novel approaches, including the use of neuroprotective agents like minocycline, are being explored to reduce secondary injury mechanisms and improve outcomes. Individualized decision-making, based on assessing the potential benefits and risks for each patient, is crucial in determining the use of thrombolytic therapy. Further research is needed to optimize patient selection, refine treatment strategies, and improve outcomes in ICH associated with thrombolytic therapy.

12. ACKNOWLEDGMENT

The author Sathya Ramanan KR, and corresponding author Satheesh S, gratefully acknowledge the Department of Pharmacy Practice, J.K.K.N College of Pharmacy, Kumarapalayam, for providing the necessary resources and support to carry out this work. We extend our heartfelt thanks to colleagues and staff at the institution for their assistance during the manuscript preparation process. The collaborative efforts of all co-authors in contributing to the research and drafting this manuscript are deeply appreciated.

13. FUNDING

No specific funding was received for this study.

14. REFERENCES

1. National Heart, Lung, and Blood Institute. Stroke. Accessed July 3, 2023. https://www.nhlbi.nih.gov/health/stroke.
2. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 20191. Lancet Neurol, 2021; 20(10): 795-820. doi:10.1016/S1474-4422(21)00252-0
3. Saposnik G, Hill MD, O'Donnell M, et al. Variables associated with 7-day, 30-day, and 1-year fatality after ischemic stroke. Stroke, 2008; 39(8): 2318-2324. doi:10.1161/STROKEAHA.107.510362
4. Khorana AA, Carrier M, Garcia DA, et al. Prevention of venous thromboembolism in cancer outpatients: guidance from ASCO and ASH [published online ahead of print, 2023 Jun 28]. Thrombosis Journal, 2023; 21(1): 56. doi:10.1186/s12959-023-00467-6
5. Khorana AA, Carrier M, Garcia DA, et al. Prevention of venous thromboembolism in cancer outpatients: guidance from ASCO and ASH [published online ahead of print, 2023 Jun 28]. J Thromb Haemost, 2023; 21(1): 56-64. doi:10.1111/jth.15627
6. Khorana AA, Carrier M, Garcia DA, et al. Prevention of venous thromboembolism in cancer outpatients: guidance from ASCO and ASH [published online ahead of print, 2023 Jun 28]. Int J Emerg Med., 2021; 14(1): 54. doi:10.1186/s12245-021-00399-w
7. The National Institute of Neurological Disorders and Stroke t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke, 1997; 28: 2109–18.
8. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). Second European–Australasian Acute Stroke Study Investigators. Lancet, 1998; 352: 1245–51.
9. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med., 2008; 359: 1317–29.
10. Sacco RL, DeRosa JT, Haley EC Jr, et al; for the Glycine Antagonist in Neuroprotection Americas Investigators. Glycine antagonist in neuroprotection for patients with acute stroke: GAIN Americas: a randomized controlled trial. Stroke, 2001; 32(8): 1802-1811. doi:10.1161/01.str.32.8.1802.
11. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence Based Clinical Practice Guidelines. Chest, 2012; 141(2): e601S – e636.
12. Lees KR, Bluhmki E, von Kummer R, et al; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet, 2010; 375(9727): 1695-1703.
13. Thrombolytic therapy: MedlinePlus Medical Encyclopedia [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2019 Feb 12; cited 2023 Jul 4]. Available from: https://medlineplus.gov/ency/article/007089.html.
14. Timely Administration of Thrombolytic Therapy in Acute Ischemic Stroke: A Review [Internet]. Graphy Publications; [cited 2023 Jul 4]. Available from:

https://www.graphyonline.com/archives/IJNCP/2020/IJNCP-331/.
15. NeurologyLive. Risk of Intracranial Hemorrhage After tPA: 5 Important Facts. New York (NY): MJH Life Sciences; [updated 2019 Jul 17; cited 2023 Jul 4]. Available from: https://www.neurologylive.com/view/risk-intracranial-hemorrhage-after-tpa-5-important-facts
16. Kwan J, Hand P, Sandercock P. A systematic review of barriers to delivery of thrombolysis for acute stroke. J Neurol Neurosurg Psychiatry, 2004; 79(10): 1093-1099. doi:10.1136/jnnp.2004.039982.
17. Saver JL. Intravenous thrombolytics in the treatment of acute ischemic stroke. Curr Treat Options Cardiovasc Med., 2022; 24(1): 4. doi:10.1007/s11936-022-00973-2.
18. Journal Article. Thrombolytic therapy. Medscape.com. Published October 17, 2021. Accessed July 4, 2023. https://emedicine.medscape.com/article/811234-overview
19. DrugBank. Streptokinase: Uses, Interactions, Mechanism of Action. DrugBank. Accessed on july 08, 2023. https://go.drugbank.com/drugs/DB00086.
20. DrugBank. Urokinase: Uses, Interactions, Mechanism of Action. DrugBank. Accessed on july 08, 2023. https://go.drugbank.com/drugs/DB00013.
21. Intracranial hemorrhage. Medscape.com. Published June 13, 2023. Accessed July 4, 2023. https://emedicine.medscape.com/article/1163977-overview
22. Mori T, Yoshioka K, Tanno Y, Kasakura S. Independent factors affecting hemorrhagic and ischemic stroke in patients aged 40-69 years: a cross-sectional study. BMC Cardiovasc Disord, 2022; 22(1): 189. doi:10.1186/s12872-022-02625-6.
23. An SJ, Kim TJ, Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: An update. J Stroke, 2017; 19(1): 3-10. doi:10.5853/jos.2016.00864
24. Brass LM, Lichtman JH, Wang Y, Gurwitz JH, Radford MJ, Krumholz HM. Intracranial hemorrhage associated with thrombolytic therapy for elderly patients with acute myocardial infarction: Results from the cooperative cardiovascular project. Stroke, 2000; 31(8): 1802-1811. doi:10.1161/01.str.31.8.1802
25. Kase CS, Furlan AJ, Wechsler LR, et al. Cerebral hemorrhage after intra-arterial thrombolysis for ischemic stroke: the PROACT II trial. Neurology, 2001; 57(9): 1603-1610.
26. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet, 2000; 355(9216): 1670-1674.
27. Larrue V, von Kummer R, del Zoppo G, Bluhmki E. Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European Cooperative Acute Stroke Study. Stroke, 1997; 28(5): 957-960.
28. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke, 2001; 32(4): 891-897. doi:10.1161/01.str.32.4.891.
29. Rost NS, Smith EE, Chang Y, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: the FUNC score. Stroke, 2008; 39(8): 2304-2309. doi:10.1161/STROKEAHA.107.512202.
30. Weimar C, Benemann J, Terborg C, et al. Prediction of malignant middle cerebral artery infarction using computed tomography-based intracerebral hemorrhage score. Stroke, 2006; 37(7): 1671-1675. doi:10.1161/01.STR.0000226606.55873.ea.
31. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet, 1974; 2(7872): 81-84. doi:10.1016/s0140-6736(74)91639-0.
32. Zhang Y, Zhang Y, Li J, et al. The association between serum uric acid and the risk of intracerebral hemorrhage: A systematic review and meta-analysis of observational studies. PLoS One, 2021; 16(3): e0248891. doi:10.1371/journal.pone.0248891.
33. UpToDate. Spontaneous intracerebral hemorrhage: Acute treatment and prognosis. UpToDate. Acessed on july 08, 2023. https://www.uptodate.com/contents/spontaneous-intracerebral-hemorrhage-acute-treatment-and-prognosis.
34. Emergency Medicine Cases. Intracerebral Hemorrhage in the Golden Hour. Emergency Medicine Cases. Acessed on july 08, 2023. https://emergencymedicinecases.com/intracerebral-hemorrhage-golden-hour/.
35. Qureshi AI, Palesch YY. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: Design, Methods, and Rationale. Neurotherapeutics, 2011; 8(3): 521-529. doi:10.1007/s13311-011-0091-8.
36. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. J Neurol Neurosurg Psychiatry, 2008; 79(10): 1093-1100. doi:10.1136/jnnp.2007.139048.
37. ICH GCP. Bleeding risk with systemic thrombolytic therapy for pulmonary embolism: scope of the problem. ICH GCP. Acessed on july 08, 2023. https://ichgcp.net/clinical-trials-registry/publications/61155-bleeding-risk-with-systemic-thrombolytic-therapy-for-pulmonary-embolism-scope-of-the-problem.

38. Mendelow AD, Gregson BA, Rowan EN, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet, 2005; 365(9457): 387-397. doi:10.1016/S0140-6736(05)17826-X
39. Sonni S, Lioutas VA, Selim MH. New avenues for treatment of intracranial hemorrhage. Curr Treat Options Cardiovasc Med., 2014; 16(1): 277. doi:10.1007/s11936-013-0277-y
40. Minocycline Accelerates Intracerebral Hemorrhage Absorption - Full Text View - Clinicaltrials.gov. Clinicaltrials.gov. Accessed July 7, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05630534
41. Zhang R, Yong VW, Xue M. Revisiting minocycline in intracerebral hemorrhage: Mechanisms and clinical translation. Front Immunol, 2022; 13: 844163. doi:10.3389/fimmu.2022.844163
42. Fouda AY, Newsome AS, Spellicy S, et al. Minocycline in acute cerebral hemorrhage: An early phase randomized trial: An early phase randomized trial. Stroke, 2017; 48(10): 2885-2887. doi:10.1161/STROKEAHA.117.018658
43. Derex L, Nighoghossian N. Intracerebral haemorrhage after thrombolysis for acute ischaemic stroke: an update. J Neurol Neurosurg Psychiatry, 2008; 79(10): 1093-1099. doi:10.1136/jnnp.2007.133371
44. McKinney JS MD, Cucchiara B MD, Assistant Professor of Neurology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Assistant Professor of Neurology, Hospital of the University of Pennsylvania. Risk scores for predicting post–thrombolysis intracerebral hemorrhage. US Neurol, 2010; 05(02): 39. doi:10.17925/usn.2010.05.02.39
45. Thrombolytic therapy. Cleveland Clinic. Accessed July 7, 2023. https://my.clevelandclinic.org/health/treatments/23345-thrombolytic-therapy.
46. Chen J, Zeng Z, Fang Z, Ma F, Lv M, Zhang J. Risk factors for thrombolysis-related intracranial hemorrhage: a systematic review and meta-analysis. Thromb J., 2023; 21(1): 27. doi:10.1186/s12959-023-00467-6
47. Cai Q, Zhang X, Chen H. Patients with venous thromboembolism after spontaneous intracerebral hemorrhage: a review. Thromb J., 2021; 19(1): 93. doi:10.1186/s12959-021-00345-z
48. EMCrit A, Farkas J. Unfractionated heparin (UFH), LMWH, fondaparinux, argatroban, and bivalirudin. EMCrit Project. Published April 3, 2023. Accessed July 7, 2023. https://emcrit.org/ibcc/heparin/
49. Unfractionated vs. Low-molecular-weight heparin for DVT. WebMD. Accessed July 7, 2023. https://www.webmd.com/dvt/unfractionated-vs-low-molecular-weight-heparin-dvt
50. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 guideline for the management of patients with spontaneous intracerebral hemorrhage: A guideline from the American heart association/American stroke association. Stroke, 2022; 53(7): e282-e361. doi:10.1161/STR.0000000000000407
51. Lee KS, Zhang JJY, Nguyen V, et al. The evolution of intracranial aneurysm treatment techniques and future directions. Neurosurg Rev., 2022; 45(1): 1-25. doi:10.1007/s10143-021-01543-z
52. McGurgan IJ, Ziai WC, Werring DJ, Al-Shahi Salman R, Parry-Jones AR. Acute intracerebral haemorrhage: diagnosis and management. Pract Neurol, 2020; 21(2): 128-136. doi:10.1136/practneurol-2020-002763
53. Patil S, Rossi R, Jabrah D, Doyle K. Detection, diagnosis and treatment of acute ischemic stroke: Current and future perspectives. Front Med Technol, 2022; 4: 748949. doi:10.3389/fmedt.2022.748949.