Introduction
Stroke is the leading cause of disability among adults globally. Despite advances in preventive strategies and initial therapy for stroke, nearly 800,000 strokes occur per year in the United States and 87% of all strokes worldwide are ischemic in origin.1 As recently as less than 10 years ago, management of acute ischemic stroke consisted of diagnosis, medical support & rehabilitation after acute event. There are now interventions for acute revascularization, either pharmacological or mechanical, that allow blood follow to be restored promptly to the ischemic brain tissue.2,3 It is also one of the leading cause of death in our country. But there has been limited progress in management of patients with stroke in developing countries and data on stroke care in these countries are sparse.4,5,6 Guidelines are continuously developed and updated in the developed world but their practicality for use in developing regions is unrealistic. The number of stroke patients receiving r-tPA in the third world is extremely low. In Stroke thrombolysis is currently used in few developing countries like Brazil, Argentina, Senegal, Iran, Pakistan, China, Thailand, and India.7 Sadly, thrombolysis is still underused in our country. Purpose of this review is to highlight the positive results of thrombolytic therapy in acute stroke which will encourage our physician to offer this therapy to an increasing number of stroke patients, and thereby reduce the considerable socioeconomic burden of stroke.

Role of Thrombolytic therapy
Ischemic stroke results from vascular occlusion that reduces cerebral blood flow to the area of brain perfused by the occluded artery. In either thrombotic or embolic stroke, such occlusion is caused by obstruction of the artery by thrombus. If the reduction in blood flow is sufficiently severe, a series of events occurs at the cellular level that leads to infarction. Tissue plasminogen activator (t-PA) is a serine protease that acts by enhancing the conversion of inactive plasminogen to active plasmin. Plasmin acts on fibrin clots, causing dissolution and lysis. The activity of t-PA is greatly enhanced in the presence of fibrin, increasing fibrinolysis specifically at the site of thrombosis.8 This theoretically result in revascularization of a previously occluded blood vessel well and reversal of brain ischemia. In vivo, t-PA is released by endothelial cells; in contrast, exogenously administered t-PA is derived from the application of recombinant DNA technology and is thus designated recombinant t-PA (rt-PA). Unlike first-generation plasminogen activators such as streptokinase and urokinase, rt-PA is fibrin-selective and preferentially activates fibrinbound plasminogen.

Thrombolytic medications in acute stroke became a significant part of stroke treatment after the publications of the National Institute of Neurological Disorders And stroke t-PA Stroke Study Group Trial (NINDS) in 1995. In this NINDS trial, the rate of a favorable outcome was significantly greater with intravenous rt-PA than with placebo (odds ratio, 1.7; 95% CI, 1.2 to 2.6; P = 0.008). This benefit was sustained at 6 months and at 1 year.9 In the subsequent ECASS III, 821 patients who presented between 3 and 4.5 hours after the onset of stroke were randomly assigned to intravenous rt-PA or placebo.10 At 90 days, significantly more patients treated with rt-PA had favorable outcomes, as compared with those given placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% CI, 1.02 to 1.76; P = 0.04).

Clinical Use of Fibrinolytic Therapy
Intravenous administration of t-PA within 3 hours after the onset of stroke increases the probability of a favorable outcome. Recommended protocols for selecting patients for treatment with intravenous rt-PA are adapted from the inclusion and exclusion criteria from the NINDS rt-PA trial. On the basis of results of ECASS III,10 some stroke centers
now treat patients who present from 3 to 4.5 hours after stroke onset; however, at present, the FDA has approved only rt-PA treatment delivered within 3 hours after stroke onset.

When a patient is evaluated for any thrombolytic therapy, it is vital to evaluate the patient as soon as practicable. In an acute setting, the patient should receive as quickly as possible:

- Triage to emergency room
- Airway, Breathing, Circulation & finger stick test to exclude hypoglycaemia
- CT scan of Head to exclude haemorrhage & to look for early signs of infarct.
- Blood Test: Complete blood count, complete metabolic panel, and coagulation profile to rule out thrombocytopenia, liver failure, and recent use of anticoagulants.
- ECG
- Evaluation of blood pressure with control using labetol or nicardipine if systolic blood pressure is 180 or greater.
- Neurological evaluation that includes:
  - Time of Onset (time the patient was last seen as normal, not time the family thinks stroke occurred)

### NIH stroke scale: Many protocols exclude patients who have mild deficits, since their prognosis for recovery is good without thrombolytic therapy.\(^\text{11, 12}\)

The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke Severity</th>
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<tbody>
<tr>
<td>0</td>
<td>No Stroke Symptoms</td>
</tr>
<tr>
<td>1-4</td>
<td>Minor Stroke</td>
</tr>
<tr>
<td>5-15</td>
<td>Moderate Stroke</td>
</tr>
<tr>
<td>16-20</td>
<td>Moderate to Severe Stroke</td>
</tr>
<tr>
<td>21-42</td>
<td>Severe Stroke</td>
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However, treatment should be initiated on the basis of the assessment of a disabling deficit rather than on a defined lower limit for the NIHSS score. For example, isolated aphasia or hemianopia is a disabling deficit despite an NIHSS score of 2 or 3.

### Inclusion and Exclusion Criteria for Intravenous t-PA Therapy in Patients with Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Diagnosis of ischemic stroke causing measurable neurologic deficit.</td>
<td>Head trauma or prior stroke within the previous 3 months</td>
</tr>
<tr>
<td>Onset of symptoms &lt;3 hr before start of treatment (or, in selected cases, &lt;4.5 hr)</td>
<td>Symptoms suggestive of subarachnoid hemorrhage</td>
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<tr>
<td>Age &lt; 18 yr</td>
<td>History of intracranial hemorrhage</td>
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<tr>
<td>Elevated blood pressure (systolic, &lt;185 mm Hg, or diastolic, e&lt;110 mm Hg) that has not responded to antihypertensive treatment</td>
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</tr>
<tr>
<td>Evidence of active bleeding on examination</td>
<td>Head trauma or prior stroke within the previous month</td>
</tr>
<tr>
<td>Seizure at onset with post-ictal residual neurologic impairments</td>
<td>Symptomatic or acute ischemic stroke within the previous 24 hours</td>
</tr>
<tr>
<td>Only minor or rapidly improving stroke symptoms (clearing spontaneously)</td>
<td>Major surgery or serious trauma within the previous 14 days</td>
</tr>
<tr>
<td>Seizure at onset with post-ictal residual neurologic impairments</td>
<td>Gastrointestinal or urinary tract hemorrhage within the previous 21 days</td>
</tr>
<tr>
<td>Acute myocardial infarction within the previous 3 months</td>
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The FDA-approved dose of intravenous rt-PA is 0.9 mg per kilogram of body weight, with a maximum dose of 90 mg. A bolus of 10% of the dose is given over a period of 1 minute, with the remainder infused over a period of 60 minutes. Weight should be determined as reliably as is possible.

Management of post-fibrinolytic period
For the first 24 hours after treatment, patients receiving rt-PA should be closely monitored in a specialized unit so that the patient can be evaluated frequently by the nursing staff. Blood pressure should be checked every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and then every hour for 16 hours. Antihypertensive therapy with labetalol or, if necessary, intravenous nicardipine should be administered to maintain blood pressure at a level below 180 mm Hg systolic and 105 mm Hg diastolic. Neurologic examination with the use of the NIHSS should be performed every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and then every hour for 16 hours. If a change in neurologic status is noted, the rt-PA infusion should be discontinued and a CT scan obtained. No anticoagulant or antiplatelet therapy should be given for the first 24 hours after treatment with intravenous rt-PA. If a CT scan at 24 hours shows no evidence of hemorrhage, antithrombotic therapy directed at secondary stroke prevention and tailored to the presumed cause of the stroke should be started.

Barrier of thrombolytic therapy
Prehospital Barriers:
One of the most important prehospital barriers of thrombolysis therapy in the developing world is nonrecognition of stroke warning signs by patients at risk, families, the general public, and even health workers in some places. There is poor recognition of stroke symptoms in developing countries. The people at the highest risk have the lowest knowledge regarding vascular disease including limitations to ascertain mild and transient symptoms as stroke. In summary, following three types of prehospital barriers identified in different studies:

- **The patient or family did not recognize symptoms of stroke or seek urgent help:** Several studies identified this as a barrier. The commonest factors associated with it were: (i) patient living alone, (ii) symptoms not recognized or not interpreted as stroke, (iii) lack of bystander witness when stroke symptoms occurred, (iv) patient or family not seeking medical help at all, (v) patient or family having no sense of urgency to seek help when symptoms started, (vi) stroke symptoms started at home, and (vii) patient refused to go to hospital.

- **Patient or family did not call an ambulance:** Twenty-three studies identified this as a barrier. These studies found that ambulance transfer was associated with a shorter delay to arrival at hospital, whereas first contacting a general practitioner (GP) increased the delay.

- **Paramedical staff did not triage stroke as an emergency:** Wefound seven studies that evaluated delays from calling the emergency services to the time of ambulance arrival, and from ambulance arrival at the patient to reaching the hospital. These studies found that stroke was often not regarded as an emergency by the paramedical staff, leading to slower ambulance transfer.

In – Hospital barrier:

- **Emergency department did not triage stroke as an emergency:** Several studies have found that examined delay from stroke onset (or arrival at hospital) to first medical assessment, neurologist assessment, or alerting the acute stroke team. The median delay from arrival at hospital to first medical assessment varied considerably, ranging from 20 minutes to 4 hours.

- **Delay in neuroimaging:** Delays occurred in: requesting the scan, transporting the patient to the radiology department, carrying out the scan, and reporting the scan by a neuroradiologist.

- **Inefficient process of in-hospital emergency department:** Reported reasons for delay in ward transfer included beds being unavailable and delay in obtaining a porter to transport the patient.

- **Difficulties in obtaining informed consent for thrombolysis:** In the acute phase, many stroke patients have language impairment or reduced consciousness, which makes it difficult to get their consent for treatment. Two studies identified this barrier. In one study, 10% of patients did not receive the treatment because they refused consent whereas only 0.4% of patients refused in another study.

- **Physicians’ uncertainty in administering rt-PA:** In the USA, where rt-PA is licensed, one study in 1998 found that only 16% of neurologists had ever administered the treatment. In this review, one study showed that some physicians were reluctant to administer rt-PA because of conflicting trial results and difficulty in starting treatment within 3 hours of stroke onset.

- **Other identified barriers:** Five studies reported other barriers: (a) delays in retrieving old medical records, performing phlebotomy, and acquiring the drug from pharmacy (b) delays in transferring the patient from another hospital.
Stroke patient is a great burden for a family as well as for the country because of huge cost of treatment and rehabilitation. So, if we give quick recovery of the patient it is beneficial for his family and the country. For this purpose we should try to overcome the barriers of treatment.

Measures to overcome these in-hospital barriers could include, e.g. training of emergency department staff to triage stroke as an emergency, improving access to CT scanning and training of doctors in administering thrombolysis.

Conclusion
Treatment with intravenous rt-PA can be given any acute ischemic stroke patients who meet the stated inclusion criteria, including presentation within 3 hours after the onset of stroke, and who do not meet any of the stated exclusion criteria. Both American Heart association and the European Stroke organization have recently updated their guidelines to extend the treatment window to 4.5 hours. So in conclusion intravenous rt-Pa is a reasonable treatment option when used in tertiary care hospital and is administered according to the guideline established by the NINDS study.

Conflict of Interest: None

References

Commonest reasons for being ineligible for thrombolysis using rt-PA,

<table>
<thead>
<tr>
<th>Reason</th>
<th>Proportion (%)</th>
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<tbody>
<tr>
<td>Delay to treatment &gt;3 hours, or onset time unknown</td>
<td>22–94</td>
</tr>
<tr>
<td>CT scan shows haemorrhage or signs of extensive infarction</td>
<td>10–22</td>
</tr>
<tr>
<td>Clinical signs of stroke too mild or resolving rapidly.</td>
<td>9–19</td>
</tr>
<tr>
<td>Medical contraindications to rt-PA</td>
<td>6–10</td>
</tr>
<tr>
<td>Refusal to consent to treatment</td>
<td>0.4–10</td>
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