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Preliminary Findings on the Efficacy and Safety of Early Intravenous Thrombolysis Administration in Acute Ischaemic Stroke Treatment

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ABSTRACT

Introduction: In Malaysia, stroke has remained the third leading cause of death after ischaemic heart disease and pneumonia from 2007 to 2017. We aimed to explore the efficacy, safety, and predictive factors of the functional outcome of early intravenous administration of recombinant tissue plasminogen activator (rt-PA), alteplase for patients who were presented to the hospital within 4.5 hours of the onset of stroke.

Methods: A longitudinal study was conducted for 36 months from January 2018 to December 2020 at Bintulu Hospital in Sarawak, Malaysia. The primary outcome was defined as the National Institute of Health Stroke Scale (NIHSS) scoring of 0 or 1, or more than an 8-point improvement in the score. The secondary endpoint was disability at 3 months post-discharge assessed using the modified Rankin scale (mRS), whereas safety endpoints were mortality, intracranial haemorrhage, and other serious adverse events. Baseline characteristics included demographics, disease-related characteristics, medication history, time of arrival to the hospital, and onset-to-needle time. Safety and efficacy data were analysed using descriptive analysis. Independent t-tests and the Chi-Square tests were used to determine predictive factors of outcomes after intravenous thrombolysis.

Results: A total of 20 participants participated in the study. We found out that 9 (45.0%) participants treated with alteplase achieved an NIHSS scoring of 0 or 1, or more than an 8-point

improvement in the score at Day 1 post thrombolysis. At 3-month follow-up, a favourable outcome of mRS $\leq$ 2 was observed in 8 participants (40.0%). Intracranial haemorrhage (ICH) and symptomatic ICH occurred in 3 (15.0%) and 1 (5.0%) participants on alteplase, respectively. Positive smoking history (P=0.01) and age group of more than 65 years old (P=0.02) were associated with poorer functional outcomes after thrombolysis.

Conclusion: Our preliminary findings showed that not all patients with acute ischemic stroke benefit from intravenous rt-PA. There is a need to identify subgroups of patients who will benefit from rt-PA, especially in resource-limited settings.

Keywords: Thrombolytic therapy, tissue-type plasminogen activator, stroke

INTRODUCTION

Stroke is a major cause of mortality and disability in many countries, including Malaysia. Global stroke estimates study reported that, in 2013, there were approximately 25.7 million stroke survivors, 6.5 million deaths, 113 million disability-adjusted life-years lost, and 10.3 million new cases of stroke (1). Department of Statistics Malaysia reported that stroke emerged as one of the top five leading causes of mortality since 2000 (1). Data in 2017 showed that cerebrovascular diseases contributed to 7.1% of all mortalities recorded in the Malaysian population (2). Intravenous alteplase (0.9 mg/kg; maximum dose of 90mg) is recommended for the definite onset stroke for up to 4.5 hours from the onset (3).

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study group reported that patients with acute ischaemic stroke who received alteplase (0.9 mg/kg of body weight) within 3 hours after the onset of symptoms were at least 30.0% more likely to have minimal or no disability at 3 months than those who received placebo (3). Two European trials, the European Cooperative Acute Stroke Study (ECASS) and ECASS II, investigated a time window of up to 6 hours but failed to show the efficacy of thrombolytic treatment, as defined by each trial (4, 5).

A subsequent analysis of the NINDS study and the combined analysis of data from six randomised trials on thrombolytic treatment for ischaemic stroke in 2775 patients, showed a clear association between treatment efficacy and the interval between the onset of symptoms and administration of the thrombolytic agent (3, 5-9). A favourable outcome was observed even if treatment was given between 3 and 4.5 hours, with an odds ratio of 1.4 for a favourable outcome with alteplase treatment as compared with placebo. This analysis also suggested that the longer time window, as compared with the shorter window, was not associated with higher rates of symptomatic intracranial haemorrhage (ICH) or death (7).

International guidelines recommend alteplase as a first-line treatment for eligible patients when administered within 3 hours after the onset of stroke (10-12). In fact, thrombolysis with alteplase has been approved for use in most countries. The European Medicines Agency (EMEA) granted approval for alteplase in 2002 on two conditions. One such condition was for an observational

safety study to be initiated. The Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS–MOST) was conducted for this reason and has subsequently proven that alteplase is safe and effective in routine clinical practice (13). The guidelines and the encouraging findings from the safety study warrant the use of alteplase, a recombinant tissue plasminogen activator (rt-PA) in eligible patients.

However, alteplase is underused despite the recommendations and findings. The underuse is more apparent in resource-limited settings, whereby fewer than 2.0% patients receive this treatment in most countries, primarily because of delayed admission to a stroke centre (14). The underutilisation of alteplase was of concern as its use in eligible patients in both safe and effective. Therefore, steps to promote its use has to be increased in all settings and limited resources should not discourage its use.

King et al analysed ischaemic stroke cases treated in Sarawak, in which modified Rankin Scales of 0-2 were observed in 57.0% patients while 6.7% died during hospitalisation (15). The study has also identified hypertension as the most prevalent risk factor for ischaemic stroke (15). The functional outcome at discharge was better and the in-hospital mortality rate was slightly lower in Sarawak when compared to the national data (15). The study by King et al opens the door to further studies analysing the ischaemic stroke treatment in different localities of Sarawak to identify the gaps in the region.

One such locality is Bintulu, a coastal town on the island of Borneo in the central region of Sarawak, Malaysia. The Bintulu Hospital provides specialist medical care with 302 beds but is without a resident neurologist. Bintulu Hospital has embarked on the use of intravenous recombinant tissue plasminogen activator (rt-PA), alteplase in the treatment of acute ischaemic stroke since 2018. All patients suitable for thrombolysis are referred to the resident neurologist in Sarawak General Hospital. Patients were then monitored by physicians after thrombolysis. This study aimed to explore the efficacy, safety and predictive factors of the functional outcome of stroke after the administration of intravenous rt-PA, alteplase in Bintulu Hospital, a hospital without a resident neurologist.

METHODS

Study Design and Participants

This was a longitudinal study conducted over 36 months from January 2018 to December 2020 at Bintulu Hospital. Patients were eligible for inclusion if they were over 18 years old, diagnosed with acute ischaemic stroke, and were suitable for thrombolysis with alteplase within 4.5 hours of symptoms onset. Cerebral computed tomographic (CT) scans were performed prior to thrombolysis to exclude patients who had ICH or major ischaemic infarction. The inclusion and exclusion criteria, additional exclusion criteria, and relative contraindication are as shown in Table 1. All study data (demographic data, NIHSS scoring, CT brain findings, and mRS score) were extracted from the electronic medical record system (ProfDoc CIS). All relevant data were entered into data collection forms for further analysis.

Table 1: Inclusion, exclusion criteria, additional exclusion criteria, and relative contraindications for thrombolysis (2)

Inclusion Criteria	Exclusion Criteria
• Clinical diagnosis of ischaemic stroke causing measurable neurologic deficit. • The onset of symptoms < 4.5 hours before beginning treatment; if the exact time of stroke onset is not known, it is defined as the last time the patient was known to be normal. • For patients presenting between 3 - 4.5 hours of onset, see additional exclusion criteria • Age >18 years old • CT scan (plain) consistent with acute ischaemic stroke	• Age < 18 years • Onset > 4.5 hours • Bleeding in computed tomography (CT) brain • Big infarct (> 1/3 of middle cerebral artery territory) • Rapidly improving or minor symptoms • Premorbid mRS ≥ 4 • Stroke or serious trauma within 3 months • Seizure at the onset of stroke (Not contraindicated if evidence suggests that residual impairments are secondary to acute ischaemic stroke and not to postictal phenomenon)

Table 1: *Continued*

Inclusion Criteria	Exclusion Criteria
	Additional Exclusion Criteria: • Age > 80 years of age • History of prior stroke AND diabetes • Any anticoagulation use before admission • NIHSS > 25 • CT findings involving more than 1/3 of middle cerebral artery (MCA) territory stroke **Relative Contraindications:** • Systolic blood pressure > 185 mm Hg or diastolic blood pressure> 110mm Hg at the time of treatment • Coagulopathy: International normalised ration (INR) > 1.7, activated partial thromboplastin time (aPTT)>1.5x normal or platelet count < 100,000 • Current use of anticoagulants: -Warfarin [unless (INR) < 1.7] -Heparin within the past 48 hours (unless aPTT < 1.5x normal) • Glucose < 2.8 mmol/L or >22 mmol/L • Pregnant (up to 10 days postpartum) or nursing mother • Symptoms of post-myocardial infarction pericarditis or known ventricular aneurysm • Peritoneal dialysis or hemodialysis

Study Treatment

In this study, alteplase was reconstituted from a lyophilised powder in sterile water for injection. 10.0% of the total dose was administered as a bolus while the remainder dose was given by continuous infusion over 60 minutes (1).

Clinical Assessment

National Institutes of Health Stroke Scale (NIHSS), a 15-item scale that measures the level of neurological impairment was used for the quantification of neurological deficit. Total scores on the NIHSS range from 0 to 42. Higher values reflect more severe cerebral infarcts. Patients were assessed with the NIHSS on day 0 and day 1. The modified Rankin Scale (mRS) was used to measure the level of disability three months after discharge. Scores on mRS range from 0 (no symptoms at all) to 6 (death). All patients suitable for thrombolysis had CT brains performed before treatment and 24 hours after treatment. Additional CT brains were performed in cases of neurological deterioration.

Outcome Measures

The primary efficacy endpoint was defined as NIHSS scoring of 0 or 1, or more than an 8-point improvement in the score from baseline at day 1 post-thrombolysis. The secondary endpoint was defined as an mRS ≤ 2 at 3 months after discharge. Safety endpoints included overall mortality, any ICH, and other serious adverse events. ECASS II definition of symptomatic ICH was any haemorrhage with neurological deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first seven days, or any haemorrhage leading to death. In addition, the haemorrhage must be identified as the predominant cause of the neurologic deterioration (5).

Statistical Analysis

Categorical variables were summarised as frequencies and percentages, while mean and standard deviation with range was calculated for continuous variables. The predictors of outcome were determined by using Independent-t and Chi-Square tests. The factors included were demographic (gender, age), risk factors such as hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, atrial fibrillation, congestive heart failure, nicotine use, systolic and diastolic blood

pressure, NIHSS score at admission and onset to needle time. Statistical analyses were performed using SPSS 26 software, IBM. inc, Texas, USA.

Sample Size Calculation

The potential patient population admitted for stroke to Bintulu hospital in 1 year was estimated to be 80. The expected proportion for sample size estimation was set at 0.4, as in 2018-2019, 122 patients were admitted to Bintulu hospital due to ischaemic stroke and only five patients were selected for thrombolysis. A sample size of 35 was calculated to achieve a precision of ±0.8 with 95.0% confidence level. Hence, all eligible patients as per inclusion criteria were enrolled in the study.

Ethical Approval

This study was registered with the National Medical Research Register (NMRR-19-2164-49718) and the ethical approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

RESULTS

A total of 387 patients with ischaemic stroke were admitted to Bintulu Hospital from January 2018 to December 2020. However, only 20 (5.2%) of the participants were suitable for thrombolysis. All of the suitable participants (n=20) were subsequently thrombolysed with alteplase.

Most of the participants were male (n=15; 75.0%) and had an average age of 59.1 years old. In terms of clinical characteristics, most of them presented to the hospital in less than 2.5 hours (n=8; 40.0%), had hypertension (n=12; 60.0%), had dyslipidemia (n=13; 65.0%) and were smokers (n=12; 60.0%). Overall, the participants had an average onset-to-needle time of 2.7 hours. The demographic and baseline characteristics of all the participants are illustrated in Table 2.

All the participants were thrombolysed within the recommended 60 minutes or less of their arrival to the hospital. The dose of alteplase used were 50 mg in 11 participants, 63 mg in 3 participants, 70 mg in 3 participants, 68 mg in 1 participant, 54 mg in 1 participant and 45 mg in 1 participant.

Table 2: Demographic and baseline characteristics (n=20)

Characteristics	Mean (SD)	Frequency (n)	Percentage (%)
Age (years)	59.1 (11.4)		
Gender			
Male		15	75
Female		5	25
Weight (kg)	64.1 (9.7)	20	100
Race			
Malay		7	35
Chinese		3	15
Iban		7	35
Others		3	15
Baseline NIHSS score	13.5 (6.2)		
0-10 (mild stroke)		9	45
11-15 (moderate stroke)		5	25
>15 (severe stroke)		6	30
Systolic pressure (mm Hg)	140.8 (19.9)		
Diastolic pressure (mm Hg)	84.7 (12.8)		
Previous use of aspirin or antiplatelet drugs		7	35
Presence of risk factors			
Diabetes		6	30
Hypertension		12	60
Atrial fibrillation		2	10
History of stroke		0	0
Dyslipidemia		13	65
Ischaemic heart disease		2	10
Congestive heart failure		3	15

Table 2: *Continued*

Characteristic	Mean(SD)	Frequency (n)	Percentage (%)
Smoking status			
Never smoked		8	40
Positive smoking history		12	60
Concurrent medications			
Antiplatelet		5	25
Anticoagulant		2	10
ACEI		2	10
Calcium channel blocker		6	30
Beta-blocker		5	25
Diuretic		4	20
Antidiabetic		4	20
Initial CT Brain findings			
Partial anterior circulation infarct (PACI)		7	35
Middle Cerebral Artery (MCA) infarct		4	20
Total anterior circulation infarct (TACI)		5	25
Lacunar infarction (LACI)		4	20
Onset to needle time (hours)	2.7 (1.2)		
<2.5		8	40
≥2.5 to ≤3.0		5	25
≥3.1 to ≤3.5		0	0
≥3.6 to ≤4.0		5	25
≥ 4.1 to ≤4.5		2	10

Efficacy

For the primary endpoint, 9 out of 20 participants (45.0%) treated with alteplase had favourable outcomes (defined as NIHSS scoring of 0 or 1, or more than an 8-point improvement in the score).

At 3-month follow-up post-discharge, a favourable outcome of mRS ≤ 2 was seen in 8 participants (40.0%) and poor outcomes including death (mRS score ≥ 3) in the remaining 12 participants (60.0%). The outcomes are illustrated in Table 3.

Table 3: Primary and secondary endpoint of the participants at 3 months post-discharge (n=20)

Endpoints	Frequency (n)	Percentage (%)
Primary Endpoint (NIHSS score of 0 or 1, or > 8 points improvements from baseline)	9	45.0
Secondary Endpoint (mRS ≤ 2)	8	40.0

Safety

A total of 3 participants (15.0%) treated with alteplase experienced ICH. Symptomatic ICH occurred in one of the participants (5.0%). Table 4 summarises the safety outcomes.

Table 4: Safety Endpoints and Other Serious Adverse Events (n=20)

Safety Endpoints	Frequency (n)	Percentage (%)
ICH	3	15.0
Symptomatic ICH	1	5.0
Fatal ICH and other serious adverse events	0	0.0

Predictive Factors of Outcome

It was found that participants above the age of 65 years old (P=0.02) and with positive smoking history (P=0.01) were significantly correlated with poor functional outcomes (mRS<2) after intravenous thrombolysis. The predictive factors of functional outcomes after alteplase administration were analysed and shown in Table 5.

Table 5*:* Predictive factors of functional outcome (mRS < 2) after intravenous thrombolysis

Variables	Favourable Outcomes (n=8); n (%)	Poor Outcomes (n=12); n (%)	t-statistics (*df*); P-value	X^2-statistics (*df*); P-value
Age, Mean (SD)	54 (9.8)	62.5 (11.5)	1.71 (18); 0.12[2]	
Age (<65 years)	8 (10.0)	5 (41.7)		5.71 (1); 0.02[b]
Gender (Male)	5 (62.5)	10 (83.3)		1.11 (1); 0.29[b]
Diabetes	2 (25.0)	4 (33.3)		0.16 (1); 0.69[b]
Hypertension	4 (50.0)	9 (75.0)		0.56 (1); 0.46[b]
Ischemic Heart Disease	0 (0.0)	4 (33.3)		3.33 (1); 0.12[c]
Atrial Fibrillation	1 (12.5)	1 (8.3)		0.09 (1); 0.76[b]
Dyslipidemia	5 (62.5)	8 (66.7)	0.18 (18); 0.86[a]	
Smoking	0 (0.0)	12 (100.0)	-1.34 (18); 0.20[a]	
NIHSS on admission, Mean (SD)	12.4 (4.0)	14.2 (7.3)	0.80 (18); 0.41[a]	
Systolic BP, Mean (SD)	133.6 (18.4)	145.6 (20.2)	-14.9 (18); 0.15[a]	
Diastolic BP, Mean (SD)	87.6 (12.2)	82.7 (13.3)		

Table 5: *continued*

Variables	Favourable Outcomes (n=8); n (%)	Poor Outcomes (n=12); n (%)	t-statistics (*df*); P-value	X^2-statistics (*df*); P-value
Onset to needle time (hours), Mean (SD)	2.2 (0.9)	3.0 (1.2)		

[a]Independent t-test

[b]Pearson chi-square test

[c]Fisher's Exact Test

DISCUSSION

Occlusion of the cerebral artery causes a critical reduction in cerebral perfusion pressure within minutes that result in a central infarct core with irreversibly damaged cerebral tissue and surrounding hypoperfused ischemic penumbra with still viable cerebral tissue. The role of thrombolytics is to salvage the ischemic penumbra by restoring the blood supply.

From our study, we found a favourable outcome of mRS score at a 3-month follow-up in 8 participants (40.0%) and an improvement in NIHSS scoring from baseline on day 1 of stroke in 9 participants (45.0%). A favourable outcome (mRS <2) was found in 39.0% participants in the NINDS trial (3). In SITS-MOST study, 54.0% participants had a good outcome, and in a study by Litwin *et al*., 61.0% participants had favourable outcomes (14, 16). The rate of symptomatic haemorrhage in our study was 5.0% as compared to 6.4% in the NINDS study and 3.3% in the Standard Treatment with Alteplase to Reverse Stroke (STARS) study (3, 17). The sample size limitation and late presentation to the hospital (> 4.5 hours from the onset of stroke) due to logistical issues may have caused our study to not have favourable outcomes in more than 50.0% participants at the 3-month follow up. However, most studies supported the use of intravenous thrombolytic therapy for acute stroke as it was associated with better functional and neurological outcomes and significantly reduces the effect of stroke morbidity and mortality.

Besides that, we found that participants below the age of 65 had favourable outcomes following intravenous thrombolytic therapy. This result was in agreement with the study by Mouradian *et al.* which reported that older patients with more severe baseline stroke had lesser benefit with intravenous thrombolytic therapy as compared to younger patients (18). A study conducted by Bandettini et.al, showed that age above 80 years old, baseline NIHSS ≥ 7, and symptomatic ICH were independently associated with mortality (19).

Several modifiable and non-modifiable risk factors can affect the outcomes of the treatment with intravenous rt-PA. Hypertension remained the most common medical risk factor for stroke, whereas current smoking and physical inactivity were the most predominant lifestyle-related risk factors (20). In general, hypertension, diabetes mellitus, and tobacco smoking tend to be more prevalent among men, whereas hypercholesterolemia, physical inactivity, and obesity were more prevalent among women (21). This was in agreement with our study results which showed that smokers had poorer outcomes (P=0.01). Other comorbidities such as dyslipidemia had also been reported to affect the outcome of patients after receiving IV rt-PA. This is due to the formation of a non-dissolvable lipid-rich thrombus, which could cause larger infarction and haemorrhagic transformation (23). From our study, about 40.0% participants with dyslipidemia had poorer outcomes but the association was not statistically significant.

The onset to needle time is crucial to the success of intravenous thrombolytic treatment. Several large trials had proved that earlier institution of rt-PA was associated with better outcomes. In our study, about two-thirds of participants in our study received rt-PA within 180 min of the onset of symptoms. A study by Demchuk *et al.* found that milder baseline stroke severity was an independent predictor of a favorable outcome following intravenous thrombolytic (22). The NIHSS score on admission was related to patients' outcomes. However, in our study which had a small sample size, we noticed that participants with NIHSS scores < 15 had better outcomes, but was not statistically significant.

Intravenous thrombolysis with rt-PA improves outcome in a selected group of patients with acute ischemic stroke but is associated with a 10-fold increased risk of symptomatic ICH (3). It is critical to select those patients who are likely to benefit from rt-PA treatment without having an increased

risk of symptomatic ICH. With regards to safety outcomes, only 5.0% of our subjects who received rt-PA treatment experienced symptomatic ICH and another 15.0% experienced ICH. This observation was consistent with previous studies, in which the incidence rates of ICH were 2.5-27.0% for acute ischaemic stroke patients treated with rt-PA (24, 25). Comparable results were also observed in Asian countries with a range of 1.9-12.1% compared with the placebo group (<1.5%) (26, 27). Fatal ICH in seven days post rt-PA treatment increased in patients treated at 3-4.5 hours after the stroke onset. However, the adverse effect of the complication was offset by increasing disability-free survival (28). Hence, the use of rt-PA for acute ischaemic stroke patients presented within 3–4.5 hours of stroke onset and under clinical observation was still an effective and tolerable measure for better functional recovery after stroke.

From our study, we can observe that the majority of the participants were not selected for thrombolysis due to late presentation to the hospital from the onset of stroke. This was largely caused by logistical issues as the majority of the patients were from neighbouring localities (Mukah, Tatau, Belaga, and Sungai Asap) at which the journey to Bintulu Hospital take hours. Hence, immediate actions are needed to improve healthcare resources for stroke care. Stroke care services encompass pre-hospital recognition, assessment and transport, acute stroke care (rapid triaging in the emergency department), rehabilitation, and community support. Post-stroke care is equally important. Primary care teams are vital to providing the majority of post-stroke care. The care of patients with stroke begins in the hospital and continues in the community, where recovery, reintegration, and health maintenance take place over the years that follow. When optimally configured, these teams provide patient-centred care to prevent recurrent stroke, maximise function, prevent late complications, and optimise quality of life.

LIMITATIONS

This study had a relatively small sample size (n=20) and was a single-centre experience. Due to the Covid-19 pandemic, the patient pool dropped drastically. Besides that, the mRS employed to examine the effect of the thrombolytic agent was an indirect outcome, rather than a direct one such as dissolution of the blood clot which may have been affected by other potential confounding factors (eg. other blood thinning medications). Future randomised controlled trials may be conducted to control these confounding factors.

CONCLUSION

Our findings show that thrombolytic therapy with intravenous rt-PA provides clinical benefits in the NIHSS score at admission and the mRS score 3 months after treatment. ICH occurred in some patients, however, no mortality or other serious adverse events were reported. Patients with positive smoking history and those who were more than 65 years old were less likely to benefit from rt-PA. However, further studies involving a larger number of more severely affected patients will be beneficial to investigate the predictive factors of outcome after intravenous thrombolysis. Actions are needed to reduce the cardiovascular burdens for stroke prevention, enhance healthcare resources for stroke care, improve post-stroke care services, and improve intravenous thrombolysis treatment in Sarawak.

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CONFLICT OF INTERESTS

All study investigators declared that they have no conflict of interest.

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REFERENCES

1. Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Roth GA, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology. 2015;45(3):161–76.

2. Aziz ZA, Lee YY, Ngah BA, Sidek NN, Looi I, Hanip MR, et al. Acute Stroke Registry Malaysia, 2010-2014: Results from the National Neurology Registry. J Stroke Cerebrovasc. 2015;24(12):2701-9.
3. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333(24):1581–1587.
4. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, Von K, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European cooperative acute stroke study (ECASS) JAMA. 1995;274(13):1017–1025.
5. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, Von K, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet. 1998;352(9136):1245- 51.
6. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA Stroke Study. Neurology. 2000;55(11):1649-55.
7. Hacke W, Donnan G, Fieschi C, Kaste M, Kummer R, Brott T, et al. Association of outcome with early stroke treatment: a pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363(9411):768-74.
8. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset — the ATLANTIS Study: a randomized controlled trial. JAMA. 1999;282(21):2019-26.
9. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Stroke. 2000;31(4):811-6.
10. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25(5):457-507.
11. National Institute for Health and Clinical Excellence (NICE). Alteplase for the treatment of acute ischaemic stroke. [Internet] June 2007 [Cited 4 July 2019]. Available from: http://www.nice.org.uk/TA122

12. Adams HP Jr, del Zoppo GJ, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007;38(5):1655-711.
13. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369(9558):275-82.
14. Albers GW, Olivot JM. Intravenous alteplase for ischaemic stroke. Lancet. 2007;369: (9558):249-50.
15. King TL, Tiong LL, Kaman Z, Zaw WM, Aziz ZA, Law WC. A hospital-based study on ischaemic stroke characteristics, management, and outcomes in Sarawak: Where do we stand? J Stroke CerebrovascDis. 2020;29(9):105012.
16. Litwin T, Kobayashi A, Skowronska M, Czlonkowska A. Thrombolysis in acute ischaemic stroke within 3 hours of symptom onset: A report of the first 100 cases. NeurolNeurochir Pol. 2008;42(1):1–5.
17. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: The standard treatment with alteplase to reverse stroke (STARS) study. JAMA. 2000;283(9):1145–50.
18. Mouradian MS, Senthilselvan A, Jickling G, McCombe JA, Emery DJ, Dean N, et al. Intravenous rt-PA for acute stroke: Comparing its effectiveness in younger and older patients. J NeurolNeurosurg Psychiatry. 2005;76(9):1234–7.
19. Bandettini PM, FinocchiC., Brizzo F, Altomonte F, Bovis F Mavilio N,. et al. Management of acute ischemic stroke, thrombolysis rate, and predictors of clinical outcome. Neurol Sci. 2019;40(2):319–326.
20. Hwong WY, Aziz ZA, Sidek NN, Bots ML, Selvarajah S, Kappelle LJ, et.al. Prescription of secondary preventive drugs after ischemic stroke: results from the Malaysian National Stroke Registry. BMC Neurol. 2017;17(1): 203.

21. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in South, East, and South-East Asia: A review. J Stroke. 2017;19(3):286-94.
22. Demchuk AM, Tanne D, Hill MD, Kasner SE, Hanson S, Grond M, et al. Predictors of good outcome after intravenous tPA for acute ischemic stroke. Neurology. 2001;57(3):474–80.
23. Urbach H, Hartmann A, Pohl C, Omran H, Wilhelm K, Flacke S, et al. Local intra-arterial thrombolysis in the carotid territory: Does recanalization depend on the thromboembolus type? Neuroradiology. 2002;44(8):695–9.
24. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359(13):1317–29.
25. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third International Stroke Trial (IST-3)): a randomised controlled trial. Lancet. 2012; 379(9834):2352–63.
26. Liao XL, Wang CX, Wang YL, Wang CJ, Zhao XQ, Zhang LQ, et al. Implementation and outcome of thrombolysis with alteplase 3 to 4.5 h after acute stroke in Chinese patients. CNS NeurosciTher. 2013;19(1):43–7.
27. Rha JH, Shrivastava VP, Wang Y, Lee KE, Ahmed N, Bluhmki E, et al. Thrombolysis for acute ischaemic stroke with alteplase in an Asian population: results of the multicenter, multinational Safe Implementation of Thrombolysis in Stroke-Non-European Union World (SITS-NEW). Int J Stroke. 2014;9(Suppl. A100):93–101.
28. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Stroke Thrombolysis Trialists' Collaborative, Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014;384(9958):1929–35.