REVIEW OF CLINICAL PREDICTORS OF HAEMORRHAGIC AND ISCHAEMIC STROKE IN EMERGENCY DEPARTMENT, HKL: AN OBSERVATIONAL STUDY

BY

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LIST OF ABBREVIATIONS

AHA	American Heart Association
BLS	Basic Life Support
CT	Computed Tomography
DBP	Diastolic Blood Pressure
ED	Emergency Department
EMS	Emergency Medical Services
ECG	Electrocardiogram
ECASS	European Cooperative Acute Stroke Study
FDA	Food and Drug Agency
GCS	Glasgow Coma Scale
HKL	Kuala Lumpur Hospital
LOC	Loss of consciousness
LAPSS	Los Angeles Prehospital Stroke Screen
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging

NIH	National Institute of Health
NINDS	National Institute of Neurological Disorders and Stroke
NIHSS	National Institute of Health Stroke Scale
PET	Positron Emission Tomography
rtPA	Recombinant Tissue Plasminogen Activator
SBP	Systolic Blood Pressure
USD	United States Dollar
U.S	United States
WHO	World Health Organization

ABSTRAK

KAJIAN MENGENAI PREDIKTOR KLINIKAL SERANGAN PENDARAHAN DAN ISKEMIA STROK DI JABATAN KECEMASAN HKL: KAJIAN PEMERHATIAN

PENGENALAN:

Kemunculan rawatan reperfusi untuk serangan akut strok iskemia telah mengubah cara rawatan serangan akut strok iskemia. Walaubagaimanapun, cara rawatan ini telah kurang berjaya disebabkan kurangnya keperhatinan di kalangan pesakit, masyarakat and kakitangan perubatan. Ini mungkin disebabkan kekurangan pengetahuan di kalangan mereka yang terlibat.

Tujuan kajian ini dibuat adalah untuk melihat tanda-tanda dan aduan-aduan biasa dalam serangan strok dan membezakan secara selamat diantara kedua-dua jenis strok. Kajian ini juga bertujuan untuk melihat masa yang diambil oleh pesakit untuk sampai di hospital.

KAEDAH:

Kajian pemerhatian hirisan lintang telah dilakukan kepada semua pesakit yang telah disahkan secara klinikal mendapat serangan akut strok yang telah dimasukkan ke HKL mulai dari Januari sehingga Mei 2005 setelah memenuhi kriteria kemasukkan dan kekeluaran. Semua pesakit mendapat pemeriksaan CT otak.

Tanda-tanda dan aduan-aduan biasa yang dikaji adalah: Umur, jantina, kaum, Glasgow Coma Scale, tekanan darah sistolik dan diastolik, pitam, sakit kepala dan muntah.

KEPUTUSAN:

Seramai seratus empat puluh tiga (Lapan puluh lapan lelaki dan lima puluh lima perempuan) pesakit telah dimasukkan untuk kajian. Enam puluh empat perpuluhan tiga peratus pesakit telah datang ke hospital selepas enam jam tanda-tanda awal strok bermula dengan majoritinya adalah pesakit strok iskemia. Pesakit strok pendarahan mempunyai kemungkinan lebih muda (mean umur lima puluh satu tahun berbanding lima puluh enam tahun), dan mempunyai tanda-tanda seperti pitam (dua puluh tiga perpuluhan satu peratus: nilai p lebih rendah dari 0.001), sakit kepala (lapan belas perpuluhan dua peratus:

nilai p lebih rendah dari 0.001), muntah (sembilan perpuluhan lapan peratus: nilai p lebih rendah dari 0.001), Glasgow Coma Scale yang lebih rendah (mean=9, Standard Deviation=2.8) dan tekanan darah sistolik yang lebih tinggi (mean 174.77, Standard Deviation=22.5).

RUMUSAN:

Prediktor yang berkesan untuk pesakit strok berkemungkinan mendapat jenis pendarahan adalah umur yang lebih muda dan mempunyai tanda-tanda seperti pitam, sakit kepala dan muntah, dan Glasgow Coma Scale yang lebih rendah dan tekanan darah sistolik yang lebih tinggi. Pesakit strok jenis iskemia mempunyai kemungkinan untuk sampai lewat, melebihi 6 jam untuk sampai ke hospital manakala pesakit strok jenis pendarahan berkemungkinan untuk sampai lebih awal, diantara 3 sehingga 6 jam.

ABSTRACT

REVIEW OF CLINICAL PREDICTORS OF HAEMORRHAGIC AND ISCHAEMIC STROKE IN EMERGENCY DEPARTMENT, HKL: AN OBSERVATIONAL STUDY

INTRODUCTION:

The emergence of reperfusion therapy in acute ischemic stroke has revolutionized the management of an acute ischemic stroke. However, this approach have been hampered by lack of urgency from the patients itself, public and medical personnels. These were probably due to lack of knowledge in current management from all involved.

Aim of this study is to review common signs and symptoms in stroke and to see if we can safely differentiate between types of stroke. This study also wants to look at time taken by each patient to arrive at Emergency Department.

METHOD:

A cross-sectional observational study for all clinically diagnosed stroke patients admitted to Hospital Kuala Lumpur from January to May 2005 after fulfilling the inclusion and exclusion criteria. All patients were subjected to brain Computed Tomography.

Common signs and symptoms on admission that were reviewed are: Age, sex, ethnic, Glasgow Coma Scale, Systolic and Diastolic blood pressure, loss of consciousness, headache and vomiting.

RESULTS:

A total of one hundred and forty-three (Eighty-eight male and fifty-five female) patients were included in this study. Sixty-four point three percent of patients presented to Emergency Department six hours after the initial symptoms started with majority of them are ischemic stroke patients. Haemorrhagic stroke patients are more likely to be younger (mean age of fifty-one years versus fifty-six years), to have symptoms of loss of consciousness (twenty-three point one percent: p value less than 0.001), headache (Eighteen point two percent: p value less than 0.001) and vomiting (nine point eight: p

value less than 0.001), and lower Glasgow Coma Scale (mean=9, Standard Deviation=2.8) and higher Systolic blood pressure (mean=174.77, Standard Deviation=22.5).

CONCLUSION:

Significant predictors for stroke patients to have higher probability of haemorrhagic type are lower age group, presented with loss of consciousness, headache and vomiting, and have lower Glasgow Coma Scale and higher Systolic blood pressure. Ischemic stroke patients are more likely to present late, more than six hours to Emergency Department while Haemorrhagic stroke patients are more likely to present earlier, within three to six hours.

CHAPTER 1

INTRODUCTION

Stroke is ranked among the top 3 leading causes of death in most countries and the leading cause of brain injury and disability in adults (Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care). Stroke inflicts a devastating physical, emotional and financial toll in its victim, their families and healthcare systems all over the world. In 1998 alone, the U.S population endured more than 600,000 strokes resulting 158,448 deaths and the loss of functional independence for countless others (AHA, 2000).

With an estimated 750,000 new strokes and more than million hospitalizations occurring in U.S each year, the importance of stroke as major cause of morbidity and mortality cannot be overemphasized. Approximately 8% of those suffering an acute stroke die within 30 days and 29% of stroke patients are dead at 1 year. Of those who survive, 16% of stroke patients require institutional care, another 31% require assistance caring for themselves and 20% of stroke survivors need walking assistance (Jauch et al., 2001). Up to one third of stroke survivors suffer from major depression and depression is common in care providers also. The direct and indirect economic impact of acute stroke in America are no less severe, with an estimated cost of USD 43 billion per year.

Until recently, care of stroke patient was largely supportive, focusing on prevention and treatment of respiratory and cardiovascular complications with little hope of affecting a positive outcome. No specific therapy was available to alter the course and extent of the evolving stroke. Therefore, little emphasis was placed on rapid transport or intervention. The last decade, however, has seen the emergence of a new treatment for acute stroke, energizing stroke care providers and spreading a sense of optimism among those who seek to alter the course of this terrible disease.

Since 1996, the US FDA has approved the use of intravenous rtPA in acute ischaemic stroke. This approval was based on the publication of 1995 results of NIH National Institute of Neurological Disorders and Stroke (NINDS) trial evaluating the use of intravenous rtPA. This trial demonstrated, for the first time, that stroke was a treatable disease in carefully selected patients who received rtPA within 3 hours of symptoms with at least 30% more likely to have minimal or no disability at 3 months compared to those treated with placebo. Fibrinolytic therapy now offers health care providers an opportunity to possibly limit the extent of neurological damage and to improve the outcome in ischaemic stroke patients. These have revolutionized the approach and urgency in management of acute stroke. The availability of neurosurgical expertise in almost all general hospitals in Malaysia also helps to minimize the extent of damage in haemorrhagic stroke.

Computed tomography have been used to confirm and differentiate the diagnosis of either haemorrhagic and ischaemic stroke (Osborn & Winthrop, 1994). CT is extremely valuable and this was recognized early on in the clinical application of diagnostic CT. In

1973, Ambrose stated "in the overall investigation of cerebrovascular disease, computerized transverse axial scanning will, without a doubt, come to be invaluable means of distinguishing between haemorrhage and infarction" (Ambrose, 1973).

CT is the study of choice for acute head injuries and for detecting spontaneous subarachnoid haemorrhage. CT is indicated once an emergency physician suspects that a structural lesion is causing the headache. CT should be done promptly on any patient if thrombolysis is applicable (Sarkarati & Reisdorff, 2002).

In the recent years, few other modalities have emerged that are more sensitive in detecting early stroke such as Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). However, due to its high cost, time-consuming and may hamper continuous observation of acutely ill patients made it unpractical as first line investigation in diagnosing stroke. The last few years, the role of CT scan have been elevated due to recent update of management on both types of stroke. Both need different approach in managing the patient and have different prognosis. Effective treatment of one stroke type may be disastrous when applied to another stroke type.

However, despite this advancement of approach in management of stroke, we are still lacking in all steps of "stroke chain of survival". This chain of survival highlights the seven step of management of stroke or **'7D's: Detection, Dispatch, Delivery, Door, Data, Decision and Drug** (AHA, 1997). The first three **'D'** represent the responsibility and awareness of Basic Life Support (BLS) providers in the community in recognising the stroke symptoms and to activate the emergency medical services. The latter four **'D'**

represents the hospital responsibility in managing patient that came with symptoms of acute stroke. These approaches are similar to patient that presents with acute myocardial infarction, which is essentially early recognition of stroke and rapid triage, evaluation in Emergency Department and definitive management. (Table 1.1)

TABLE 1.1 STROKE CHAIN OF SURVIVAL OR SEVEN 'D's

(Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care).

Detection	Awareness of stroke signs and symptoms by the patient or bystanders
Dispatch	Activation of EMS systems, priority dispatch and rapid EMS response
Delivery	Rapid transport to the appropriate facility, en-route assessment and prehospital notification
Door	Emergency department triage
Data	Emergency department evaluation
Decision	Selection of appropriate therapy and intervention
Drug	Delivery of therapeutics

Performing an extensive neurological examination outside the hospital is impractical. As such, stroke screen or scale has been used with much success in the U.S. These stroke scales have been validated and most cities have its own. Two of most common and extensively used are Cincinnati Prehospital Stroke Scale (Table 1.2) (Kothari et al.,1999) and Los Angeles Prehospital Stroke Screen (LAPSS) (Table 1.3) (Kidwell et al.,2000). The Cincinnati Scale is used to elicit any of the 3 major physical findings suggestive of stroke: Facial droop, arm drift and abnormal speech (Kothari et al., 1999). LAPSS requires the examiner to rule out other cause of altered level of consciousness and then identify asymmetry in facial smile/grimace, grip or arm strength. Asymmetry in any category indicates a possible stroke (Kidwell et al., 1998, Kidwell et al., 2000). These two scales are sensitive and specific in identifying stroke patients (Kidwell et al., 1998, Kothari et al., 1999, Kidwell et al., 2000). Either evaluation can be performed quickly.

TABLE 1.2 CINCINNATI PREHOSPITAL STROKE SCALE

	Normal	**Abnormal**
Facial droop (Have patient show teeth or smile)	Both sides of face move equally well	One side of face does not move as well as the other side
Arm drift (Have patient close eyes and hold both arms straight out for 10 seconds)	Both arms move the same or both arms do not move at all	One arm does not move or one arm drifts down
Abnormal speech	Correct words with no slurring	Patient slurs words, use the wrong words or is unable to speak

TABLE 1.3 LOS ANGELES PREHOSPITAL STROKE SCREEN (LAPSS)

For evaluation of acute, non comatose, non traumatic neurological complaint: if items 1 through 6 are ALL checked "YES" (or unknown), notify the receiving hospital before arrival of the potential stroke patient. If any are checked "NO", follow appropriate treatment protocol

Interpretation: 93% of patients with stroke will have positive findings (all item checked "YES" or "unknown") on the LAPSS (sensitivity=93%) and 97% of those with positive findings will have a stroke (specificity=97%). The patient may still be having a stroke if LAPSS criteria are not met.

CRITERIA	YES	UNKNOWN	NO
1. Age > 45 years			
2. History of seizures or epilepsy absent			
3. Symptom duration < 24 hours			
4. At baseline, patient is not wheelchair bound or bedridden			
5. Blood glucose between 60 – 400			
6. Obvious asymmetry in any of the following 3 categories (must be unilateral) • Facial smile/grimace • Grip • Arm strength	Equal	R Weak	L Weak

TABLE 1.4 NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKES (NINDS) RECOMMENDED STROKE EVALUATION TARGETS FOR POTENTIAL THROMBOLYTIC CANDIDATES

(Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care).

Time interval	Time target
Door to doctor	10 minutes
Access to neurological expertise	15 minutes
Door to CT completion	25 minutes
Door to CT interpretation	45 minutes
Door to treatment	60 minutes
Admission to monitored bed	3 hours

** Target times will not be achieved in all cases, but they represent a reasonable goal

CHAPTER 2

OBJECTIVES

2.1 AIM:

1. To evaluate time taken for each stroke patient from the initial symptoms to assessment by doctors.
2. To review the presenting symptoms that is commonly associated with haemorrhagic stroke.
3. To review the presenting signs that is commonly associated with haemorrhagic stroke.
4. To review the presenting symptoms that is commonly associated with ischemic stroke.
5. To review the presenting signs that is commonly associated with ischemic stroke.

2.2 SELECTION OF PATIENTS

All patients with haemorrhagic and ischaemic stroke (confirmed by CT scan brain) that are admitted to HKL during the study period.

2.2.1 Inclusion criteria

- Clinical diagnosis of stroke
- Non trauma case
- Age > 18 years

2.2.2 Exclusion criteria

- Referred case
- Trauma case
- Age < 18 years
- Recurrence of stroke
- History of serious head trauma
- Alcohol intoxication
- History of brain pathology (other than vascular in origin)
- Blood glucose level < 3.5 mmol/L

2.3 RESEARCH HYPOTHESIS

i. Majority of patients presented more than 6 hours after initial symptoms

ii. Patient that presented to Emergency Department, HKL with stroke cannot be safely differentiate types of stroke based on clinical presentation alone

2.4 DEFINITION

Stroke :

- Rapidly developed clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin. (WHO)
- Results from any disease process that disrupts vascular blood flow to a distinct region of brain (Tintinalli et al., 2000)

CHAPTER 3

LITERATURE REVIEW

3.0 BACKGROUND

Effective treatment of the patient who has sustained an acute ischaemic stroke requires rapid assessment and early intervention. The window of time for therapy, as determined on the basis of animal and human studies, is limited to the first few hours after the onset of stroke. Currently, only thrombolysis with recombinant tissue plasminogen activator (rtPA) within 3 hours of stroke onset has been shown to be beneficial (NINDS, 1995).

The early treatment of stroke is complicated by several potential systemic delays. Patients and families may be unaware of the clinical manifestations of stroke and as a result may not seek emergency care. Emergency medical personnel may triage stroke victims to a low priority, resulting in delay in transport and evaluation. Imaging with computed tomography (CT) may not be immediately available. Therapeutic nihilism with regard to stroke in the general medical community may preclude rapid triage and treatment. Emergency and primary care physicians may rely on consultation with neurologists to treat patients with focal deficits. Neurologists tend to concentrate on a careful history and treatment to localize and classify a neurologic lesion but typically are not trained in rapid diagnosis and treatment (Kasner & Grotta, 1997). Similar roadblocks

were perceived when thrombolysis was a new treatment for acute myocardial infarction (MI) (Sharkev et al., 1989; Gonzalez et al., 1992).

However, most centres now adhere to the minimum time-to-treatment recommendations established by the American Heart Association Emergency Cardiac Care Committee and the National Heart Attack Alert Programme Coordinating Committee, and eligible acute MI patients are given thrombolytic agents within 30 – 60 minutes of arrival. The Brain Attack Coalition, supported by the American College of Emergency Physicians, the American Academy of Neurology and the National Stroke Association, seeks to improve both public and medical education regarding the importance of time.

3.1 PATHOPHYSIOLOGY

Pathophysiology of ischaemic stroke was the basis of management of acute stroke, which was a complex but consistent series of events that occurs after abrupt interruption of cerebral blood flow. It is a dynamic process that depends on both the severity of ischaemia and its duration. The ischaemic cascade starts within seconds to minutes of loss of perfusion, such that obstruction of blood vessels creates a central area of irreversible infarction and a surrounding area of potentially reversible "ischaemic penumbra". (Hossman, 1994; Fisher & Garcia, 1996). The penumbral region is fundamentally salvageable and is therefore the ultimate target of therapy.

At the cellular level, protein synthesis initially ceases as the ischaemic neuron attempts to conserve its rapidly waning energy stores. Membrane ion-transport systems fail and the neuron becomes depolarized. Membrane depolarization results in calcium influx, which in turn causes release of stores neurotransmitters. Glutamate, the major excitatory neurotransmitter in the brain, is released in large quantities. It worsens the cellular insult by further increasing intracellular calcium and by depolarizing other metabolically compromised neurons. Other neurotransmitters may also intensify the injury. The massive calcium influx stimulates several enzymes, which becomes unregulated and may cause destruction of cellular homeostatic mechanisms, cytoskeleton, mitochondria and cell membrane. Free radical formation and nitric oxide synthesis may further contribute to neuronal damage.

During the hours to days after a stroke, the ischaemic territory activate specific genes. Formation of cytokines and cell adhesion molecules stimulates local inflammation and may further impair blood flow in the microcirculation. Finally, apoptotic gene activation may promote programmed cell death in the population of surviving neurons. Without timely intervention, the entire ischaemic penumbra eventually succumbs to these progressive insults and becomes confluent with the infarct core.

In human beings, the presence of an ischaemic penumbra may be detected through the use of positron emission tomography (PET) (Heiss & Herholz, 1994; Marchal et al., 1996) and the magnetic resonance techniques of diffusion- and perfusion-weighted imaging. (Rother et al., 1996; Warach et al., 1996; Fisher et al., 1995). Detailed descriptions of these methods are beyond the scope of this review, but they provide evidence for the existence of an ischaemic penumbra surrounding an infarct core in patients who have sustained acute strokes. Furthermore, these techniques demonstrate that in most cases the penumbra merges with the infarct core within several hours of the onset of stroke. (Heiss & Herholz, 1994; Marchal et al., 1996)

On this basis of current understanding of ischaemic cascade and the evolving penumbra, it appears that acute intervention must occur very early for a substantial portion of brain tissue to be preserved. Subsequently, several animal studies were done which suggested reperfusion must occur within 3 hours. (Marchal et al., 1996;

Minematsu et al., 1992). Preliminary results from human imaging studies also suggest similar time frame.

As such, the only proven effective therapy for acute stroke also mandates a 3-hour window for perfusion. The time window in which to alter the course of the ischaemic cascade remains less well defined, but it is also presumed to be relatively brief. (Aronowski et al., 1996). However, the cascade comprises many points at which intervention may be attempted.

3.2 MAJOR ACUTE STROKE TRIALS

The two major strategies for the treatment of acute stroke are restoration of cerebral perfusion and neuronal protection. However, only trials of reperfusion by means of thrombolysis have demonstrated a positive benefit.

Restoration of cerebral blood flow after an acute vascular occlusion may be achieved by the administration of thrombolytic agents. rtPA and streptokinase are of proven efficacy in acute MI and are the most extensively studied agents for thrombolysis in stroke. However, as demonstrated by the results of several major trials, only rtPA has a favourable risk-to-benefit profile in the treatment of stroke.

The specific choice of thrombolytic drug for the treatment of acute stroke depends on several pharmacokinetic factors. Although both rtPA and streptokinase convert plasminogen to plasmin, which in turn causes cleavage of fibrin and ultimately results in lysis of a clot, the two agents have different mechanisms of action. rtPA specifically activates plasminogen that is already bound to a thrombus, whereas streptokinase activates unbound circulating plasminogen, causing systemic depletion of fibrinogen. The effects of streptokinase are therefore much longer-acting and less clot-specific than those of rtPA but rtPA effects significantly more rapid lysis than streptokinase in coronary trials (Anderson & Wilierson, 1993). In the treatment of acute MI, streptokinase does not necessarily require the concurrent use of heparin because of its induction of a prolonged

lytic state, but rtPA has a relatively brief effect in the absence of concurrent heparin (Anderson & Wilierson, 1993). Streptokinase is substantially less expensive than rtPA.

The timing of thrombolysis is of paramount importance. As described earlier, ischaemic brain tissue may be salvageable if reperfusion occurs before the tissue is irreversibly damaged. Moreover, the risk of haemorrhage appears to increase once the ischaemic tissue becomes oedematous (Hacke et al., 1997; von Kummer et al., 1997). On the basis of findings from animal studies and preliminary human studies, the National Institute of Neurological Disorders and Stroke (NINDS) rtPA study used a 3-hour limit for initiation of therapy. In the other trials of rtPA and streptokinase, patients were given the agents between 3 and 6 hours after the onset of stroke.

The European Cooperative Acute Stroke Study (ECASS) 1995 was a randomized, prospective, multicentre, double-blind, placebo-controlled study of 620 patients who had sustained acute ischaemic hemispheric stroke. Patient were randomized to receive treatment with intravenous rtPA 1.1 mg/kg or placebo within 6 hours of the onset of stroke. The median time from stroke onset to treatment was 4.3 hours. The primary endpoints were the Barthel Index (a 100-point scale of independence with regard to activities of daily living) and the Modified Rankin Scale (a 5-point scale of disability) at 90 days. No significant benefit of rtPA over placebo was noted in the overall intention-to-treat analysis with regard to the primary endpoints. However, 109 patients (17.4%) included in this analysis were considered protocols violations and should have been barred from enrolment because they fulfilled at least one exclusion criterion. In the

remaining patients referred to as the target population, a significant improvement in Rankin Scalescore was evident at 90 days. Furthermore, several secondary endpoints--including the combined Barthel and Rankin scores, speed of neurologic recovery and the length of hospital stay—were significantly improved by rtPA in both the intention-to-treat and target-population analyses. Although rtPA-treated patients had a higher incidence of parenchymal intracerebral haemorrhage (19.8% versus 6.5%; P<0.001), no significant difference was found in mortality at 30 days between the rtPA and placebo groups (17.9% versus 12.7%; not significant) in either analysis (Kasner SE & Grotta, 1997).

Most protocols violations were the result of enrolment of patients with CT exclusion criteria: major signs of early infarction, primary haemorrhage, or unreadable/unavailable CT scan. Patients in the protocol-violation group who were treated with rtPA had a much higher risk of haemorrhage and death than those given placebo. On the basis of the differences between intention-to-treat and the target-population analyses, the authors concluded that treatment of an unselected stroke patient population within 6 hours of stroke onset is not recommended.

The NINDS rtPA stroke study was a randomized, prospective, multicentre, double-blind, placebo-controlled study of 624 patients who had sustained acute ischaemic stroke. Patients who fulfilled the inclusion and exclusion criteria (refer Table 3.1) were randomly assigned to receive intravenous rtPA 0.9 mg/kg or placebo within 3 hours of the onset of symptoms. Half of the patients were treated within 90 minutes. The study

was divided into 2 parts, each with a specific primary endpoint. In part 1, the effect of rtPA within 24 hours of stroke, was measured on the basis of complete resolution of deficit or improvement of at least 4 points on the National Institute of Health Stroke Scale (NIHSS, a 42-point scale of specific neurologic deficits); 3-month outcome was a secondary endpoint. On the basis of the analysis of part 1, part 2 was designed to assess the benefit of rtPA at 3months as determined by a global statistic comprising the Barthel Index, Modified Rankin Scale, Glasgow Outcome Scale and the NIHSS. Investigators remained blinded to the results of part 1 until both parts were completed. Part 1 failed to demonstrate a significant effect of rtPA on the primary endpoint at 24hours, although rtPA was associated with significant improvement in the median NIHSS at 24 hours in the secondary analysis and 3-month outcome was also improved. Part 2 demonstrated significant improvement in clinical outcome at 3 months in patients treated with rtPA in the global statistic and in each of its 4 individual components.

Overall, the odds ratio for a favourable outcome in the rtPA group was 1.7 (95% confidence interval, 1.2 to 2.8; P=0.008). This result was achieved with a relatively smaller study size than the trials of thrombolysis for MI, and was both statistically significant and clinically robust. The absolute increase in the number of patients with minimal or no deficit in part 2 was 11% (relative benefit, 55%) by the NIHSS and 13% (relative benefit, 50%) by the Rankin Scale. The benefit of rtPA was realized regardless of the presumed cause of stroke: large-vessel occlusive disease, small-vessel occlusive disease and cardioembolism. The rate of symptomatic intracerebral haemorrhage in the first 36 hours was significantly greater in the patients treated with rtPA than in those

given placebo (6.4% versus 6%; P<0.001), but there was no significant difference in mortality at 3 months (17% versus 21%; not significant).

The division of the NINDS rtPA trial into two parts has created some confusion in the medical community. Each part was essentially independent of the other and each had a unique hypothesis but the methods were identical and the data were published together. Many expected that if thrombolysis was beneficial, it should have had an early rather than a late effect at 3 months. This assumption might yield the conclusion that the negative results of part 1 should therefore cast the findings of the overall analysis into doubt. Such a conclusion is unwarranted. The specific hypothesis of part 1—that rtPA would cause a 4-point improvement on the NIHSS or complete resolution of symptoms within 24 hours—was not supported by the statistics. There was no significant difference in the proportion of patients with early improvement or excellent outcome in the rtPA (47%) and placebo groups (39%). However, when median NIHSS scores were evaluated , there was 4-point difference in favour of the rtPA treated group (NIHSS, 12; placebo,8; P< 0,02). A similar benefit was observed in the 24-hour outcome of the patients in part2 of the study (Kasner SE & Grotta, 1997).

Because of the methodologic differences between the NINDS and ECASS studies, direct comparisons are limited. The major difference was the acute time frame. The use of rtPA is therefore only recommended when therapy can be initiated within 3 hours. However, as intimated by the ECASS analysis of the target population, careful selection of patients with appropriate CT criteria may eventually allow for treatment

beyond 3 hours. Although the CT criteria for the NINDS trial only excluded patients with haemorrhage, a retrospective analysis of the ECASS data suggests that major early infarct signs should be considered a contraindication to the rtPA treatment in any time frame (Hacke et al.,1997; von Kummer et al., 1997). These early CT changes may indicate that the time of onset is earlier than reported or that the injured brain tissue is already beyond the point of recovery. The sequelae of subtle CT changes are less clear, and they should not be considered a contraindication to therapy in the 3 hours immediately after the stroke Kasner SE & Grotta, 1997). The European study also used a higher dose of rtPA than did the NINDS study.

INCLUSION CRITERIA	1. Age > 18 years 2. Clinical diagnosis of ischaemic stroke, with onset of symptoms within 3 hours of initiation of treatment 3. CT (non-contrast) without evidence of haemorrhage
EXCLUSION CRITERIA	**Historical** 1. Stroke or head trauma in previous 3 months 2. History of intracranial haemorrhage 3. Major surgery or other serious trauma in previous 14 days 4. Gastrointestinal or genitourinary bleeding in previous 21 days 5. Lumbar puncture in previous 7 days 6. Pregnant or lactating female **Clinical** 1. Rapidly improving stroke symptoms 2. Seizure at onset of stroke 3. Symptoms suggestive of subarachnoid haemorrhage even if CT is normal 4. Persistent systolic BP > 185 or diastolic BP >110 mm Hg or requiring aggressive therapy to control BP 5. Clinical presentation consistent with acute MI or post-MI pericarditis, requires cardiologic evaluation prior to treatment **Radiographic** 1. CT evidence of haemorrhage 2. CT with evidence of hypodensity and/or effacement of cerebral sulci in more than one third of middle cerebral artery territory **Laboratory** 1. Glucose < 50 or > 400 mg/dl 2. Platelets < 100,000/mm^3 3. On warfarin, and prothrombin time (PT) > 15 seconds 4. On Heparin therapy within 48 hours, and partial thromboplastin time (PTT) is elevated

TABLE 3.1 Inclusion and exclusion criteria for thrombolysis of acute ischaemic stroke (Multicentre Acute Stroke Trial- Italy (MAST-I), 1995)

Three major trials in Streptokinase have demonstrated that it is neither beneficial nor a safe treatment for acute ischaemic stroke when coronary doses are given up to 6 hours after stroke onset. All three trials were randomized, prospective, multicentre studies and all three were terminated before completion because of unacceptable mortality rates.

In the Multicentre Acute Stroke Trial – Italy (MAST-I), 622 patients with acute ischaemic stroke were randomized within 6 hours of stroke onset. Patients received intravenous 1.5 megaunits Streptokinase or Aspirin 300 mg daily for 10 days, both or neither. Neither streptokinase, nor aspirin, nor the combination significantly improved outcome. Streptokinase was also associated with significant increase in the 10-day mortality rate compared with controls (27% versus 12%; $P<0.00001$), although the incidence of haemorrhage with streptokinase alone (6%) was similar to that found with rtPA in the NINDS study.

The Multicentre Acute Stroke Trial – Europe (MAST-E) enrolled 310 patients within 6 hours of the onset of symptoms. Patients received either intravenous streptokinase 1.5 megaunits or placebo. Approximately two thirds of patients also received concomitant treatment with heparin, many within the first 12 hours after the administration of streptokinase or placebo. There was a non significant trend toward less disability, as measured with the Rankin Scale, in patients who received streptokinase. However, mortality was greater in those treated with streptokinase than in those given placebo, both at 10 days (34% versus 18.2%; $P=0.002$) and 6 months (46.8% versus 38.3%; $P=13$; not significant)

The Australian Streptokinase (ASK) trial recruited 340 patients within 4 hours of onset of acute stroke. Patients were randomized to receive placebo or treatment with intravenous streptokinase 1.5 megaunits. Aspirin was also administered whenever possible. Overall, streptokinase afforded no benefit with regard to outcome on the Barthel Index at 3 months and it was associated with significantly increased risk of intracerebral haemorrhage (13.2% versus 3% with placebo; $P<0.01$). Mortality at 3 months was also significantly greater with streptokinase (36.2% versus 20.5%; $P<0.05$). However, these poor outcomes were predominantly attributable to treatment after 3 hours. Among the 70 patients treated during the 3-hour window, the authors noted a non significant trend toward improved outcome without excess mortality.

Thrombolysis is an effective therapy for acute stroke, but only one thrombolytic agent, rtPA, has proven efficacy and safety. Early and rapid assessment is essential because treatment must begin in the 3 hours after onset. Patients must be selected on the basis of rigid adherence to the inclusion and exclusion criteria to limit the risk of haemorrhagic complications. Careful evaluation of the initial CT scan also appears to be important in reducing the risk of intracranial haemorrhage. Finally, the concurrent use of anticoagulant and antiplatelet agents must be strictly avoided for the first 24 hours. Continuing research is focused on methods to better identify those patients who may benefit most from thrombolysis with rtPA, as well as on improved means to exclude those at highest risk for haemorrhagic complications (Kasner & Grotta, 1997).