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Intravenous Tissue Plasminogen Activator (IV tPA) Use in Acute Ischemic Stroke Patients in Michigan

By

Yingzi Deng

A THESIS

Submitted to
Michigan State University
In partial fulfillment of the requirements
For the degree of

MASTER OF SCIENCE

Department of Epidemiology

College of Human Medicine

2003

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ABSTRACT

INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR (IV TPA) USE IN ACUTE ISCHEMIC STROKE PATIENTS IN MICHIGAN

By

Yingzi Deng

Limited information is available to assess why eligible acute stroke patients do not receive IV tPA. The objective of this study was to identify factors associated with IV tPA use among eligible patients. A total of 2566 acute stroke patients were identified from May to November 2002 in the Michigan Acute Stroke Care Overview & Treatment Surveillance System (MASCOTS), a state-wide registry. Eligible patients for IV tPA were defined as those arriving within 3 hours of symptom onset with no evidence of hemorrhage on initial CT image and no physician documented contraindications. Patients who were excluded from analysis included: 469 who had hemorrhagic signs on initial CT images, 793 who had no stroke onset time documented, 851 who arrived at the ED greater than three hours after stroke onset, and 123 patients who either had rapidly improving symptoms, or mild strokes, or had other physician documented exclusions. Among the remaining 330 patients, 43 received IV tPA (13%). Being female, arriving by EMS, and earlier hospital presentation were associated with a significantly higher likelihood of receiving IV tPA. Most acute stroke patients were ineligible for IV tPA either because stroke onset time was not documented or they presented outside the 3-hour therapeutic window. Among those who arrived within 3 hours, transportation via EMS and arrival within the first hour of onset was strongly associated with IV tPA use.

To my husband, Mingquan, and my love daughter, Leilei

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LISTS OF ABBREVIATIONS

ASK	Australian Streptokinase Trial
ATLANTIS	Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke
BI	Barthel Index
CI	Confidence Interval
ECASS	European Cooperative Acute Stroke Study
ED	Emergency Department
IA	Intra-arterial
ICH	Intracerebral Hemorrhage
ITT	Intention-to-treat
IV	Intravenous
MASCOTS	Michigan Acute Stroke Care Overview & Treatment Surveillance System
MAST	Multicenter Acute Stroke Trial
MRS	Modified Rankin Scale
NINDS	National Institute of Neurological Disorders and Stroke
PROACT	Prolyse in Acute Cerebral Thromboembolism Trial
SIF	Suspect Stroke Intake From
STARS	Standard Treatment with Activase to Reverse Stroke Study
TP	Target Population
tPA	Tissue Plasminogen Activator

CHAPTER 1

INTRODUCTION

1.1. Epidemiology of stroke in US and Michigan

Although stroke mortality rates have declined by 70 percent since 1950 [1], stroke still entails an enormous burden of mortality, morbidity, disability and health care costs in the United States.

1.1.a. Mortality

An estimated 167,661 people died of stroke in 2000 and stroke is the nation's third leading cause of all mortality, accounting for 7% of all deaths. From 1990 to 2000, the death rate from stroke declined 12.3 percent, however the actual number of stroke deaths rose 9.9 percent because of the increasing older population [2]. African-Americans have a higher risk of dying from stroke than Caucasians. The 2000 stroke death rates per 100,000 population were 58.6 for white males, 87.1 for black males, 57.8 for white females and 78.1 for black females [2]. In Michigan, stroke resulted in a similarly heavy burden, accounting for 5,789 deaths or 6.7% of all deaths in 2000 [3]. Michigan had the 18th highest overall stroke mortality rate in the US [4]. One in eight stroke deaths occurred in individuals under age 65. Eighty seven percent of those dying from stroke were Caucasian and 12% were African-American.

1.1.b. Morbidity

Each year about 700,000 people experience a new or recurrent stroke [5]. About 500,000 are first attacks, and 200,000 are recurrent attacks. The age-adjusted stroke incidence rates (per 100,000) for first-ever strokes are 167 for white males, 138 for white

females, 323 for black males and 260 for black females. Blacks have almost twice the risk of first-ever stroke compared with whites [5]. Sixty percent of all stroke victims were women. Of all strokes, 88 percent are ischemic, 9 percent are intracerebral hemorrhage, and 3 percent are subarachnoid hemorrhage [2]. According to the National Heart, Lung, and Blood Institute's (NHLBI) Framingham Heart Study, 28 percent of stroke patients are under age 65. The risk of stroke mortality increases rapidly with age; the incidence of stroke more than doubles in each successive decade after age 55 until age 85. Men have a higher risk of dying of stroke than women, but more women die of stroke because more women live to the oldest age groups [6].

1.1.c. Long-term Consequences of Stroke –Disability, Hospitalization and Costs

Stroke is the leading cause of long-term severe disability in USA [2]. About 4.7 million stroke survivors are alive today. From the early 1970s to early 1990s, the estimated number of institutionalized stroke survivors increased from 1.5 to 2.4 million [6]. In 1999, more than 1.1 million American adults reported difficulty with functional limitations, activities of daily living, etc., resulting from stroke [7]. The length of time to recover from a stroke depends on its severity. Fifty to seventy percent of stroke survivors regain functional independence, but 15 to 30 percent are permanently disabled. Twenty percent still require institutional care at three months after onset [7].

Total annual costs (direct and indirect) of stroke are enormous. More than 981,000 stroke hospital discharges occur each year. Stroke costs the United States $30 to $40 billion per year [2]. From 1979 to 2000, the number of Americans discharged from short-stay hospitals with stroke as the first listed diagnosis increased 31.3 percent [2]. In 1998, $3.6 billion ($5,912 per discharge) was paid to cover costs of care for Medicare

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beneficiaries discharged from short-stay hospitals for stroke [8]. In Michigan, there were 37,405 hospital admissions for stroke (2.9% of all admissions) in 2000 [3].

1.2. Overview of Recanalization Treatment of Acute Ischemic Stroke

1.2.a. Recanalization strategies

The most common subtype of stroke is ischemic stroke, which is caused by acute occlusion of a cerebral blood vessel, initiating a series of events, which can lead to irreversible neuronal damage and cell death (i.e. infarction) in the part of the brain supplied by the obstructed vessel. Thus, restoration of blood flow to the ischemic brain as soon as possible after cerebral vessels have been occluded may lessen the volume of brain damaged by ischemia, reduce the likelihood of major cerebral edema, and result in better clinical outcomes. Thrombolytic agents that can effectively recanalize occluded vessels and restore blood flow have been extensively studied. Thrombolytic agents can be delivered either intra-arterially (IA) or intravenously (IV).

1.2.b. Thrombolytic Therapy- intra-arterial (IA)

IA thrombolytic therapy refers to the delivery of thrombolytic agent either by regional infusion or by local infusion directly into thrombus using supra-selective catheters. This approach has the potential advantage of increased recanalization rates by delivering higher concentrations of drug and enhances the safety because of a reduction in the total dose of drug administered. In the Prolyse in Acute Cerebral Thromboembolism Trial (PROACT) I and PROACT II study, 246 patients were randomized within 6 hours of symptom onset to receive either 9 mg prourokinase plus heparin or heparin alone [9, 10]. Complete or partial reperfusion was significantly higher

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in treated patients than that of control. A statistically significant better outcome (modified Rankin score$\leq$ 2) was seen in treated group at 3 months compared with that of control patients. The symptomatic ICH rate was higher in the treated group as compared with the control group, while there was no significant difference at the 90-day mortality rate. Although both studies showed moderate benefit for patient treated with prourokinase, Food and Drug Administration (FDA) requested further studies for its efficacy and safety.

One major disadvantages of this IA approach are the logistic delay of treatment because of the requirement for angiography, increased cost, decreased availability of facilities, and personnel that might limit its generalizability. A geographic analysis indicated that only 37% of US population had access to IA thrombolysis if 3-hour time window were to be met whereas access to IV thrombolysis was nearly universal [11].

1.2.c. Thrombolytic Therapy- intravenous (IV)

At present, the majority of data from clinical testing of thrombolytic agents in ischemic stroke has focused on the use of IV thrombolysis. Although there are various kinds of IV thrombolytic agents, tissue plasminogen activator (tPA) and streptokinase (SK) are the two that have been most extensively tested in acute ischemic stroke. Three randomized, double-blinded, placebo-controlled trials of streptokinase in the treatment of acute ischemic stroke were conducted in mid-nineties: the Multicenter Acute Stroke Trial-Italy (MAST-I) [12], the MAST-Europe (MAST-E) [13], and the Australian Streptokinase Trial (ASK) [14]. Streptokinase was given at a dose of 1.5 million units (the full cardiac dose). MAST-I and MAST-E treated patients up to 6 hours after stroke onset, while Australian Streptokinase Trial treated patients within 4 hours. All three were

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stopped prematurely because of excess mortality and intracranial hemorrhage, although the ASK Trial did find a trend toward benefit in patients treated within 3 hours of onset.

1.3. Overview of Randomized Clinical Trials of IV tPA and FDA Approval:

As a result of the safety concerns and limited efficacy data related to streptokinase and prourokinase, trials using IV tPA now became the mainstream of thrombolytic agents underwent intensive testing for acute ischemic stroke treatment.

tPA, which is produced using recombinant DNA technology, is a fibrinolytic agent that has considerably higher fibrin specificity than streptokinase or urokinase for plasminogen activation [15]. Eight IV tPA trials for stroke have been reported so far; 2 in Japan, 1 in Europe, 1 involved collaborations of several Western countries and 5 in US.

Two Japanese Trials of tPA in acute ischemic stroke were conducted in 1988 and 1993 with relative small sample size (n=89) [16, 17]. Both supported the efficacy of intravenous infusion of tPA in the treatment of acute ischemic stroke within 6 hours of onset, and also demonstrated that IV tPA was generally safe and was associated with better outcomes than conventional treatment. But their small sample size and different tPA product limited the comparability and generalizability of their study results.

The European Cooperative Acute Stroke Study (ECASS-I) [18] was a multi center, double-blinded, placebo-controlled trial conducted in Europe between late 1992 and early 1994 at 75 centers in 14 European countries [18]. Six hundred and twenty patients with acute hemispheric stroke were randomized within 6 hours of onset to receive either tPA (1.1mg/kg, maximum dose 100mg) or placebo. Primary endpoints were measured using Barthel Index (BI) and the modified Rankin Scale (MRS) 3 months after stroke. Both intention-to-treat (ITT) and Target Population (TP, patients without

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protocol violations) analysis were completed. There was no significant difference in the BI and MRS at 3 months using ITT. When the 15% of patients with protocol violation (n=109) were excluded, a statistically significant benefit in favor of tPA was seen on the MRS at 3 months in the remaining TP. There were no statistically significant differences in the 30-day mortality rates. But the incidence of major parenchymal hematoma was 19.8% in tPA group vs 6.5% in the control group ($p<0.001$). They concluded that tPA might be effective in improving some functional and neurological measures in the subgroup of stroke patients with moderate to severe neurological deficit and without extended infarct signs on the initial CT scan. But IV tPA within 6 hours could not be recommended for use in an unselected populations of patients with acute ischemic stroke because the treatment carries excessive risk and selection of appropriate patients was difficult even at academic centers.

In the United States, a series of trials funded by the National Institute of Neurological Disorders and Stroke (NINDS) were conducted and demonstrated the efficacy and safety of IV tPA for acute ischemic strokes when used within 3 hours of symptom onset. After a preliminary IV tPA administration protocol was setup by a pilot study in 1990 [19], the NINDS tPA Trial was conducted as 2 consecutive trials that started in 1991 and reported together as Part 1 and Part 2 in one publication [20]. A pretreatment CT scan was conducted to exclude patients with intracerebral hemorrhage. Eligible patients were then randomized to receive tPA at a dose of 0.9 mg/kg (maximum of 90 mg) or placebo. Part 1 was designed to test the early improvement 24 hours after tPA treatment with 291 patients enrolled, part 2 was to determine whether functional improvement was better at 3 months in the treated patients (N=333). In part 1, no

significant difference between tPA and placebo was identified in the primary outcomes (improvement by 4 or more in the NIHSS score or a complete resolution of the neurologic deficit). In part 2, significant improvement at 3 months was observed in the treatment group. As evaluated by global statistic, the odds ratio (OR) for favorable outcome in the tPA group was 1.7 (95% CI: 1.2 to 2.6, p=0.008). TPA patients were at least 30 percent more likely to have minimal or no disability (a score of 95 or 100 on the Barthel Index) at 3 months compared with placebo group. Symptomatic ICH during the first 36 hours after treatment was higher in tPA patients than that of the placebo (6.4% vs 0.6%, p<0.001). The mortality rate at three months was 17% in the tPA group and 21% in the placebo group (p=0.3). Thus, the NINDS tPA Study Group concluded that despite increased incidence of symptomatic ICH, treatment with IV tPA within 3 hours of onset of ischemic stroke improved clinical outcome at three months. Post hoc analysis of NINDS tPA trial data further suggested that patients treated 0 to 90 minutes from stroke onset had better outcomes compared to patients treated later than 90 minutes [21].

Efforts to further evaluate the efficacy of IV tPA therapy beyond the 3-hour window were undertaken in two additional randomized trials: ECASS-II [22] and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke study (ATLANTIS) [23, 24]. Both trials did not find significant difference in mortality or functional outcomes between treatment group and placebo, but the rate of symptomatic ICH was significantly higher among tPA-treated patients. Therefore, these studies did not support the use of IV tPA therapy more than 3 hours after stroke onset.

Among these five randomized controlled trials of tPA discussed above, only the NINDS trial demonstrated significant beneficial functional outcomes and none of the 5

studies showed a mortality benefit. In 1996, the Food and Drug Administration (FDA) approved the use of tPA among acute ischemic stroke patients within 3 hours of stroke onset mainly based on the results of the NINDS trial.

Meta-analysis and systematic review of the data from these clinical trials further demonstrated that IV tPA was beneficial to the functional outcomes at three months but increased the ICH rate and early mortality after the treatment, and the patients treated within 3 hours of stroke onset had better outcomes. In 1997, Wardlaw et al. conducted a meta-analysis evaluating the thrombolytic therapy given 6 hours after acute ischemic stroke onset. Thrombolytic therapy was associated with a significant excess of mortality and ICH rate. In contrast, in the cohort of patients treated within 3 hours of stroke onset, there was a significant reduction in the number of patients who were dead or dependent at the end of follow-up. Five trials have data available related to IV tPA therapy and 1257 patients were enrolled in these five trials [16-18, 20, 25]. The total case fatality in tPA trials with different tPA dosages were similar with other types of thrombolytic agents (i.e. urokinase, streptokinase). Thus, Wardlaw et al. believed that thrombolytic therapy require further testing in large randomized trials because the risk seems substantial and the benefit uncertain. Another meta-analysis was conducted by Hacker et al. that included data from three major tPA trials: NINDS, ECASS-I and ECASS-II. Overall, 2044 patients were enrolled in the three trials combined. After adjusting various definitions of outcomes across trials, and limiting analysis only to the patients treated within 3 hour of symptom onset (n=866), the overall odds of ICH was 2.68. The odds ratio for mortality was 0.91 and there was a very significant reduction in the rate of dependence, from 71.6% in placebo treated patients to 57.7% in tPA treated group (OR, 0.55; 95%CI: 0.41-

0.72) [26]. In the recent Cochrane systematic review of thrombolysis in acute ischemic stroke, seventeen trials of four kinds of thrombolytics including 5216 patients were analyzed. IV tPA trials contributed 2,889 patients, or 56% of the data [27]. Overall, thrombolytic therapy significantly increased the odds of death within the first ten days (OR=1.85, 95%CI: 1.48-2.32). The main cause of death was fatal ICH following thrombolysis (OR=4.15, 95%CI: 2.96-5.84). Symptomatic ICH increased after tPA therapy (OR=3.53, 95%CI: 2.79-4.45). Despite the risks, thrombolytic therapy administered up to 6 hours significantly reduced the proportion of patients who were dead or dependent (OR=0.83, 95%CI: 0.73-0.94). For the patients treated within 3 hours of stroke, the results favored the thrombolytics even more (OR=0.58, 95%CI: 0.46-0.74) [27].

1.4. Guidelines of IV tPA Use in Acute Ischemic Stroke

After approval of IV tPA therapy for acute ischemic stroke by the FDA, National Institute for Neurologic Disorders and Stroke, the Stroke Council of the American Heart Association and the American Academy of Neurology soon published practice guidelines to strongly advocate the use of tPA in acute ischemic stroke [28-30]. Despite these guidelines and FDA approval, substantial controversy prevented the widespread use of tPA for ischemic strokes in routine clinical practice. The American College of Emergency Physicians (ACEP) waited for six years after FDA approval before publishing its first guidelines for tPA therapy for acute ischemic stroke in 2002 [31]. They based their guidelines on the evidence not only from the NINDS trial but also from more than 8 open label safety studies of IV tPA conducted afterwards [32]. ACEP stated that: " Intravenous tPA may be an efficacious therapy for the management of acute

ischemic stroke if properly used incorporating the guidelines established by the National Institute of Neurological Disorders and Stroke (NINDS)", but there was "insufficient evidence at this time to endorse the use of intravenous tPA in clinical practice when systems are not in place to ensure that the inclusion/exclusion criteria established by the NINDS guidelines for tPA use in acute stroke are followed". Also, in the Policy Statement by American Academy of Family Physicians, they emphasized that "therapy with tPA for acute ischemic stroke is effective and of overall benefit, but it carries risk" [33]. Across the world, tPA therapy for acute ischemic stroke was approved only in USA and Canada, and with a strict license in Germany. The Canadian Stroke Consortium and the Royal College of Physicians of London published their guidelines for tPA treatment in acute ischemic stroke in 1998 and 2000, respectively [34, 35], with a more cautious attitude towards tPA therapy. These guidelines recommended treating acute ischemic stroke patients whose onset of symptoms were known to be <3 hours, to use tPA at a dose of 0.9 mg/kg (maximum dose 90mg), with 10% of the dose given as a bolus followed by an infusion over 60 minutes. Recently, the Stroke Council of the American Stroke Association updated their guidelines for thrombolytic therapy, as cited in the following table (Part A and Part B) [36]. Adherences to the guidelines are crucial, as recent studies have shown that protocol violation increase the risk of symptomatic ICH after thrombolysis [37].

Part A. Characteristics of Patients With Ischemic Stroke Who Could Be Treated With tPA [36]
• Diagnosis of ischemic stroke causing measurable neurological deficit • The neurological signs should not be clearing spontaneously • The neurological signs should not be minor and isolated • Caution should be exercised in treating a patient with major deficits

- The symptoms of stroke should not be suggestive of subarachnoid hemorrhage
- Onset of symptoms <3 hours before beginning treatment
- No head trauma or prior stroke in previous 3 months
- No myocardial infarction in the previous 3 months
- No gastrointestinal or urinary tract hemorrhage in previous 21 days
- No major surgery in the previous 14 days
- No arterial puncture at a noncompressible site in the previous 7 days
- No history of previous intracranial hemorrhage
- Blood pressure not elevated (systolic <185 mm Hg and diastolic <110 mm Hg)
- No evidence of active bleeding or acute trauma (fracture) on examination
- Not taking an oral anticoagulant or if anticoagulant being taken, INR $\leqslant$1.5
- If receiving heparin in previous 48 hours, aPTT must be in normal range
- Platelet count $\geqslant$100 000 mm3
- Blood glucose concentration$\geqslant$50 mg/dL (2.7 mmol/L)
- No seizure with postictal residual neurological impairments
- CT does not show a multilobar infarction (hypodensity >1/2 cerebral hemisphere)
- The patient or family understand the potential risks and benefits from treatment

Part B. Regimen for Treatment of Acute Ischemic Stroke Intravenous tPA) [36]

- Infuse 0.9 mg/kg (maximum of 90 mg) over 60 minutes with 10% of the dose given as a bolus dose over 1 minute.
- Admit the patient to an intensive care unit or a stroke unit for monitoring.
- Perform neurological assessments every 15 minutes during the infusion of tPA and every 30 minutes for the next 6 hours and then every hour until 24 hours from treatment.
- If the patient develops severe headache, acute hypertension, nausea, or vomiting, discontinue the infusion (if agent is still being administered) and obtain a CT scan of brain on an emergent basis.
- Measure blood pressure every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and then every hour until 24 hours from treatment.
- Increase the frequency of blood pressure measurements if a systolic blood pressure $\geqslant$180 mm Hg or diastolic blood pressure of $\geqslant$105 mm Hg is recorded. Administer antihypertensive medications to maintain blood pressure at or below these levels.
- If diastolic blood pressure 105–120 mm Hg or systolic blood pressure 180–230 mm Hg, intravenously administer 10 mg labetalol over 1–2 minutes. May repeat or double the dosage or labetalol every 10 to 20 minutes to a maximum dose of 300 mg. As an alternative, can start with the initial bolus dose of labetalol and then follow with a continuous labetalol infusion given at a rate of 2–8 mg/min.
- If diastolic blood pressure 121–140 mm Hg or systolic blood pressure$\geqslant$ 230 mm Hg, intravenously administer 10 mg labetalol over 1–2 minutes. May repeat or double labetalol every 10 minutes to a maximum dose of 300 mg. As an alternative, can start with the initial bolus dose of labetalol and then follow with a

continuous labetalol infusion given at a rate of 2–8 mg/min. If the blood pressure is not controlled, consider starting an infusion of sodium nitroprusside.

- If diastolic blood pressure $\geqslant$ 140 mm Hg, start infusion of sodium nitroprusside at a rate of 0.5 mg/kg/min.
- Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters.

1.5. Use of IV TPA in Clinical Practice

It has been seven years since the FDA approved IV tPA therapy for acute ischemic stroke in the United States. A number of centers have contributed data of their experience with the use of IV tPA in daily clinical practice. Most sites have used the NINDS protocol and have treated patients within the 3-hour time window. The majority of the studies demonstrate that more favorable outcomes are seen in tPA treated patients compared with those not treated. While conflicting results were reported with regard to safety and feasibility of tPA therapy in Standard Treatment with Activase to Reverse Stroke Study (STARS) [38] and Cleveland Area Experience study [39].

In the STARS study published in 2000, the largest case series currently reported, 389 patients were treated with tPA in 24 academic and 33 community medical centers across the United States from February 1997 to December 1998. The thirty-day mortality rate was 13%, which was comparable to that of the NINDS trial. Thirty-five percent of tPA treated patients had favorable outcomes (MRS: 0-1) and 43% were functionally independent (MRS: 0-2) at 30 days after treatment. The rate of symptomatic ICH after thrombolysis was 3%. Protocol violations were seen among 32.6% of the tPA patients. This study suggested that favorable clinical outcomes and low rates of symptomatic ICH could be achieved using tPA for stroke treatment in clinical practice [38]. Almost at the same time, a retrospective cohort study was conducted in the community setting in 29

Cleveland area hospitals [39]. The Cleveland Area Experience published in 2000 reported that only 1.8% ischemic stroke patients received IV tPA. The rate of symptomatic ICH was 15.7% in 79 tPA treated patients. Fifty percent had protocol violations; in-hospital mortality was significantly higher among patients treated with IV tPA (15.7%) compared with patients not receiving IV tPA (5.1%, $p<0.001$). Thus, they concluded that only a small proportion of patients received IV tPA and these patients experienced a high rate of ICH. Differences between these two studies include their study designs (prospective in STARS vs retrospective in Cleveland), pre-treatment stroke severity adjustment (poor documentations of NIHSS scores in Cleveland experience) and different clinical settings (more experienced centers in STARS). All the 57 participating medical centers in STARS were part of an ongoing randomized clinical trial (ATLANTIS study) and all of the principal investigators were neurologists who had previous experience treating patients with tPA or placebo in the setting of clinical trial. While hospitals in Cleveland Area Experience had less experience treating patients with tPA. These conflicting results suggest that tPA therapy in non-stroke specialized hospitals may differ from that given in experienced centers or in those reported in clinical trials [39]. In a recent published Cleveland Update, they reported that after a Quality Improvement (QI) program was implemented in Cleveland area hospitals in 1999, the percentage of acute ischemic stroke patients that received tPA increased slightly (47/1727, or 2.7%), but the protocol violations decreased significantly to 19.1%. The rate of symptomatic ICH also dropped to 6.4%. They concluded that the QI project was effective in increasing the safety and use of the tPA in community-based clinical practice [40].

Since these two reports, a series of studies have reported their experiences regarding tPA with respect to safety, outcomes and feasibility of use in acute stroke patients outside of clinical trial settings. Table 1.1 provides an overview of these 12 new studies [41-50]. Except in the Cleveland Area Experience, which reported the highest symptomatic ICH rate so far (15.7%), the rest of the studies reported similar rates as that of NINDS trial, i.e. around 6%. The NINDS trial identified that ischemic signs on baseline CT scan and stroke severity >20 on the NIHSS score were two predictors of serious ICH [51]. Lopez-Yunez et al examined the association between protocol violations and outcomes in community-based settings. Fifty patients were treated with tPA according to NINDS trial protocol in this study. Protocol violations were observed in 8 patients. ICH within 36 hours of tPA administration was more frequent among patients with protocol violations compared to those without (38% vs 2.4%, $p<0.01$). When the NINDS protocol was strictly followed, hemorrhagic rates were similar to those in the NINDS trial [37]. Protocol violations were relatively common in routine clinical practice. STARS investigators detected protocol violations in 32.6% of 389 tPA treated patients, more than half of these violations were due to treatment given beyond the three hour window. However no significant association was found between protocol violations and the rate of symptomatic ICH in STARS. This lack of association was also reported in the Cleveland area experience. They reported high rates of protocol violations (50%), and again treatment given beyond three-hour window was the most common violation. These results imply that ICH risk depends more on the type of protocol violation, and that time violations per se might be not as serious as other contraindications, such as anticoagulation use or elevated blood pressure during the 24 hours after tPA treatment.

With regard to mortality rate after tPA treatment, the updated Cochrane systematic review by Wardlaw et al. indicated that in clinical trials there was no significant difference in early mortality between tPA treated and placebo patients [27]. While in the routine clinical practice settings, data to determine the association between in-hospital mortality rate and tPA treatment was conflicting. Cologne and OSF stroke Network both suggested that tPA therapy did not increase in-hospital mortality rate [41, 48]. While the in Cleveland Experience Study [39] and in a study by Reed et al [52] in-hospital mortality was higher among tPA patients. Recently, the German Stroke Registry Study Group evaluated the risk of in-hospital mortality among acute ischemic stroke patients with regard to tPA use [49]. After control for propensity scores, which was used to balance the non-random design in the observational studies, the overall in-hospital mortality was still higher for the patients that received tPA (OR=1.7, 95%CI: 1.0-2.8). Patients receiving tPA in less experienced centers (administered ≤ 5 thrombolytic therapy in 2000) had an increased risk of in-hospital mortality (OR=3.3, 95% CI: 1.1-9.9). Their study suggested that tPA therapy in hospitals with limited experience in tPA treatment had adverse effect on outcomes.

One fact that is clear from the literature review is that there has been no substantial increase in the percent of ischemic stroke patients receiving tPA treatment in the United States since 1996. TPA use ranged from 1.8% to 9% of all ischemic stroke patients in these studies. Major reasons for this underutilization of tPA include: 1) The 3 hour treatment window is too short for a majority of patients to present in time for medical care [43, 53], 2) Lack of infrastructure for appropriate administration of tPA within 3 hours [54], and 3) Physicians' concern about the efficacy and safety of tPA

treatment [43, 55, 56]. In an analysis of patient eligibility by Barber et al, they found that 73% of acute ischemic stroke patients were excluded because they presented to the ED after 3 hours of onset. Of the remaining 27% of patients who presented within 3 hours, 27% received tPA therapy but a further 31% were excluded because their symptoms were either considered too mild or were rapidly improving. Overall, only 7.2% of acute ischemic strokes finally received tPA [47]. Other studies also reported similar findings with regard to ineligibility of tPA treatment among ischemic stroke patients [45, 57]. Among patients apparently eligible for tPA therapy (i.e. no contraindications documented) and who arrived within the 3-hour treatment window, there is still a very large proportion of patients who do not receive tPA. However very limited data is available regarding the factors associated with tPA use among these apparently eligible patients.

1.6. Summary

Stroke is a serious disease that entails an enormous burden of mortality, morbidity, disability and health care cost in the United States. Ischemic stroke accounts for 80 percent of all stroke cases. Thrombolytic treatments to recanalize the occluded blood vessels have been shown to decrease the infarct size and result in better neurological functional outcomes. Even though there are multiple thrombolytic agents available, tissue plasminogen activator is the only one approved by the FDA for use in ischemic stroke. Besides randomized clinical trials of IV tPA, clinical case series reports on tPA use have shown that the long-term outcome of tPA treated patients are better than patients not receiving tPA, and in experienced centers tPA therapy can be delivered safely. But the uncertainty of its efficacy, the concerns of the risk the therapy carried and

the very narrow treatment time window limited its wide spread use, with less than 5% of acute stroke patients receiving IV tPA. Thus it would be beneficial to investigate the factors that are associated with the tPA use among eligible patients.

1.7 Thesis Rationale

Thesis objectives

The objective of this study is to use data from the Michigan Acute Stroke Care Overview & Treatment Surveillance System (MASCOTS) to assess IV tPA use for acute ischemic stroke in a representative sample of Michigan hospitals and patients, to identify factors associated with its use among eligible patients, and to review the safety of IV t-PA treatment in these settings.

Specific questions

1) Determine the proportion of ischemic stroke patients that were eligible for tPA treatment and to determine the rate of IV tPA use among them.
2) Investigate factors associated with receiving tPA therapy among eligible ischemic stroke patients.
3) Review the safety of tPA therapy by documenting the frequency of major complications and protocol violations.
4) Document the processes of care (including the proportions of acute stroke patients that met the NINDS recommended time intervals etc) and in-hospital outcomes among tPA treated cases.

Table 1.1 Summary of Literature Review.

Paper source	Study design /Setting	TPA Use (%)	Reason of Ineligibility	Safety	Outcome
NINDS	Multicenter randomized Clinical trial	Part 1: 291 Part 2: 333	NA	Total ICH rate=11% Symptomatic ICH rate=6% Mortality rate at 3 month=17%	BI: 50%(100-95) MRS: 39%
Cologne, Stroke, 1998; 29:1544	Prospective open-label study: with 14 community hospital and university hospital with referral system (97/3-97/5)	100/453 (22%)presumed stroke	Misdiagnosis 10.6% Hemorrhagic sign on CT: 18.5% Rapid improvement: 16.8% Arrival later than 3 hours: 21.1% Predefined exclusion criteria: 10.3%	Total ICH rate=11% Symptomatic ICH rate=5% Fatal ICH rate= 1% Mortality rate at 90days=12%	NIHSS: 42% (0-1) BI: 53%(100-95) MRS: 40% (0-1)
Chiu et al; Stroke 1998 29: 18-22	Prospective open-label monocenter study: Experienced center (95/12-96/12)	30/ 267 suspected stroke (6%)	Beyond 3-hour time limit (37%), ICH (22%), Minor or rapidly resolving symptoms (19%), A no stroke diagnosis (12%).	Total ICH rate= 10% Symptomatic ICH rate=7% Fatal ICH rate= 3% Mortality =23%	BI: 37%(100-95) MRS; 30% (0-1)
Multicenter survey, Neurology, 1999; 53:424-427	Retrospective survey in 13 hospitals with stroke triage system (96/1-97/12)	189	NA	Total ICH rate= 9% Symptomatic ICH rate=6% Fatal ICH rate= 2%	NA
Berlin. Stroke 32: 1074-1078	Prospectively recruited patients (98/5-00/04)	75 /504 IS (14.9%)	Time of onset unknown (40%) Arrive later than 3 hours (28%)	Fatal ICH rate= 2.7% Mortality rate =15%	BI: 61% MRS: 40%
Cleveland Experience. JAMA, 283; 1151-1158	Historical prospective cohort study (97/7-98/6)	70/3948 with ICD9: 434,436(1.8%)	3-hour treatment window 17% arrived at ED < 3hours	Total ICH rate= 22% Symptomatic ICH rate=15.7% Fatal ICH rate= 8.6% In-hospital mortality=15.7%	%Discharge ome=28.6%

Paper source	Study design /Setting	TPA Use (%)	Reason of Ineligibility	Safety	Outcome
STARS study. JAMA.2000: 283:1145-1150	Prospective, multicenter study (97/2-98/12)	N=389	NA	All ICH rate= 8.2% Symptomatic ICH rate=3.3% Fatal ICH rate=1.8% 30 day mortality rate=13%	MRS: 35%
Why are stroke patients excluded from tPA therapy? Neurology 2001; 56:1015-1020	Consecutive patients with acute ischemic stroke were prospectively identified	84/1168(7.4%)	ED beyond 3 hours excluded 73.1% 27% admitted within 3 hours, Within this group: Mild stroke (13.1%), Clinical improvement (18.2%) Perceived protocol exclusion (13.6%), ED delay (8.9%) Significant comorbidity (8.3%)	NA	NA
The OSF Stroke Network. Stroke. 2000; 31:77-81.	Prospective cohort (96/6-98/12)	57/900(6.3%)	NA	ICH rate = 9%; Symptomatic. ICH=5%	MRS= 47% NIHSS=44% Discharge home= 54%
Houston Experience. Arch Neurol; 2001; 58:2009-2013	Prospective /retrospective: in a large urban setting (96/1-00/6)	269 (9%)	152/1757=8.7%	Symptomatic ICH rate=5.6% In-hospital mortality=15%	NA
Helsinki; Stroke. 2003; 34:1443-1449	Case series (98/3-01/10)	75 /3498 (2.1%)	NA	Symptomatic ICH= 8% Mortality = 5%.	BI: 61% MRS: 37%

Paper source	Study design /Setting	TPA Use (%)	Reason of Ineligibility	Safety	Outcome
A Cleveland Update. Stroke 34: 799-800	A retrospective chart review after a stroke quality improvement program in 1999.	47/ 1923 (2.7%)cases with ICD-9 codes 434 and 436	Only 288(14.9%) out of 1923 arrived within 3 hr window.	Symptomatic ICH =6.4% Protocol violation =19.1%	NA
A Canadian Hospital's Experience; stroke, 2000; 31:2920-2924.	A combined retrospective and prospective review	46/ (1.8%) consecutive patients treated with	NA	Symptomatic ICH =2.2% In-hospital mortality=22%	Transferring patients had longer onset to treatment time (173 vs. 148) but shorter door to needle time (43 vs. 102).
German ADSR. *Stroke.* 2003; 34:1106	Prospectively regional based stroke registry	384 /13440 IS patients (3%).	NA	In-hospital mortality =11.7%	NA

CHAPTER 2

METHODS

2.1 MASCOTS Study

2.1.1 Overall design

The Michigan Acute Stroke Care Overview & Treatment Surveillance System (MASCOTS) was designed as a representative, statewide, hospital-based surveillance system of acute stroke care in Michigan. MASCOTS is a multi-centered project based at Michigan State University that involves collaboration with two other major universities (University of Michigan and Wayne State University), the Michigan Department of Community Health, and a total of sixteen hospitals across the state. The primary objective of MASCOTS was to develop and refine the methods and infrastructures necessary to conduct long-term surveillance of acute stroke care and stroke outcomes in the state of Michigan.

2.1.2 Sampling of State Hospitals:

MASCOTS was implemented in 16 Michigan hospitals in two phases. In order to test case ascertainment protocols and data collection instruments, a pilot study (Phase I) was conducted in 8 hospitals of 4 regional sites (Detroit, Washtenaw County, Ingham County, and Kalamazoo) from January to March in 2002. These 8 Phase I hospitals are referred to as stratum 1 that have a probability of one to be selected in subsequent Phase II. Following this pilot phase, MASCOTS was expanded to include 16 statewide hospitals by the inclusion of 8 Phase II hospitals from 4 additional strata.

Stratum 1 consisted of the 8 Phase I hospitals that were selected regardless of their number of stroke discharges. In order to obtain a representative sample of hospitals in the state of Michigan, stratified sampling was used to select the 8 phase II hospitals from the additional 4 strata. The initial sampling frame consisted of a list of 106 Michigan hospitals that provided care to at least 30 stroke cases in year 2000. The estimate of the number of acute stroke admissions to each hospital was based on the number of discharges with a primary diagnosis of stroke (ICD-9 codes: 430-438). Stratified random sampling proportional to size, i.e., the number of stroke discharges in 2000, was used to select 2 hospitals from each of 4 strata. In order to include smaller community-level hospitals from rural areas, we first defined a stratum consisting of the 52 hospitals in counties that had 30 to 361 stroke discharges in year 2000. This stratum is referred as stratum 5 (Table 2.1). The remaining 54 hospitals were then divided into three equal sized strata in terms of the total number of stroke discharges (each stratum therefore had approximately 8,700 discharges – see Table 2.1). Stratum 2 included 7 large hospitals that had between 795 and 1,741 stroke discharges in year 2000. Stratum 3 consisted of 14 hospitals that had between 541 and 791 stroke discharges, and stratum 4 consisted of 33 hospitals that had between 38 and 521 stroke discharges in year 2000 (Table 2.1). Thus, the 16 hospitals selected in MASCOTS represented 26% (9,457) of the 36,000 stroke discharges statewide in year 2000 (Table 2.2). These 16 hospitals were believed to be a representative sample of hospitals in the state of Michigan in terms of its urban, suburban and rural communities and key demographic characteristics of its population are shown in Figure 2.1.

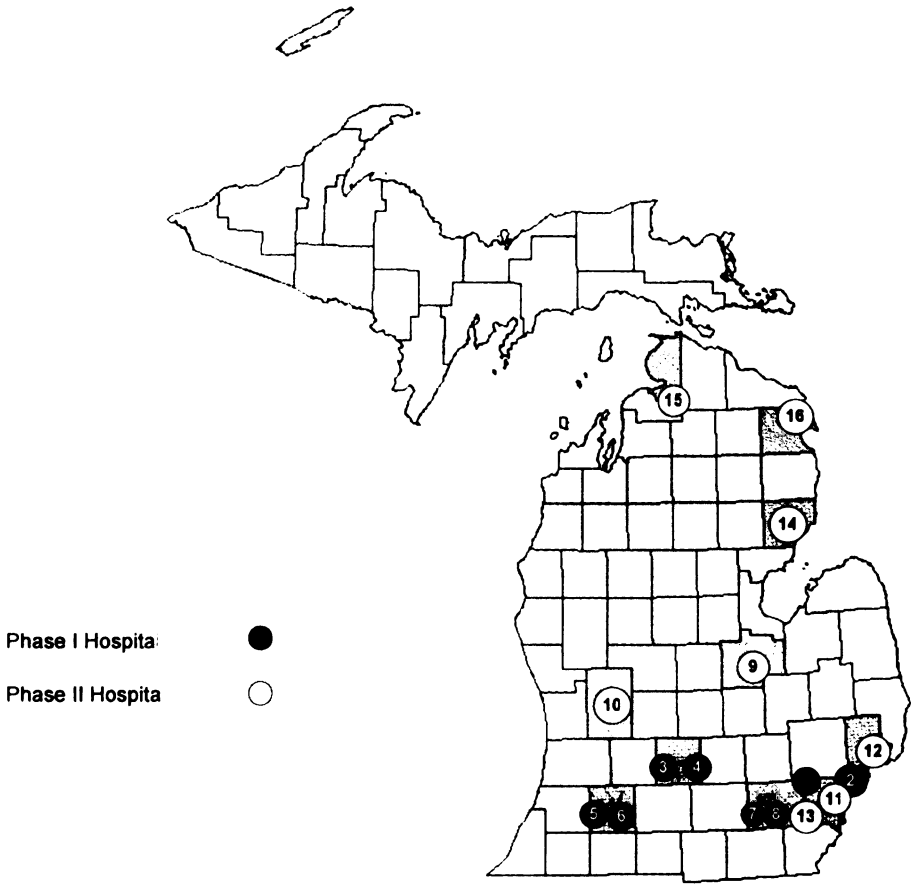
Table 2.1. Summary of Stratified Sampling

Stratum	Number of Hospitals in the Stratum	Location of Hospitals (County)	Range of Stroke Discharges (Lowest – Highest)	Total Number of Stroke Discharges in Stratum	Percent of all Statewide Stroke Discharges in Stratum
1	8	Wayne, Washtenaw, Kalamazoo, Ingham	357 ~ 878	5,072	14%
2	7	Kent, Saginaw	795 ~ 1,741	8,341	23%
3	14	Macomb, Oakland	541 ~ 791	8,740	24%
4	33	Wayne, Emmet	38 ~ 521	8,746	24%
5	52	Iosco, Alpena	38 ~ 361	4,982	14%

Table 2.2 Identity and Characteristics of the 16 MASCOTS Registry Hospitals

Hospital	Discharges	City	County
Phase I (Stratum 1)			
Harper University Hospital	678	DETROIT	WAYNE, MI
Detroit Receiving Hospital	461	DETROIT	WAYNE, MI
Ingham Regional Med Center	499	LANSING	INGHAM, MI
Sparrow Hospital & Health System	700	LANSING	INGHAM, MI
Borgess Medical Center	878	KALAMAZOO	KALAMAZOO, MI
Bronson Methodist Hospital	357	KALAMAZOO	KALAMAZOO, MI
SJMHS St. Joseph Mercy-AA	860	ANN ARBOR	WASHTENAW, MI
University of Michigan Hospital	639	ANN ARBOR	WASHTENAW, MI
Sub-total (Phase I)	**5,072**		
Phase II			
Stratum 2			
St. Mary's Hospital - Saginaw	795	SAGINAW	SAGINAW, MI
Spectrum Health - Grand Rapids	1,456	GRAND RAPIDS	KENT, MI
Stratum 3			
Henry Ford Wyandotte Hospital	554	FERNDALE	OAKLAND, MI
St. Joseph Mercy-Macomb	660	CLINTON TOWN	MACOMB, MI
Stratum 4			
Riverside Osteopathic Hospital	214	TRENTON	WAYNE, MI
Northern Michigan Regional Health System	438	PETOSKEY	EMMET, MI
Stratum 5			
St. Joseph Health System-Tawas	80	TAWAS CITY	IOSCO, MI
Alpena General Hospital	188	ALPENA	ALPENA, MI
Sub-total (Phase II)	**4,385**		
Grand Total	**9,457**		

Figure 2.1 Phase I and Phase II MASCOTS Hospital Map



2.1.3 Case Ascertainment

Prospective case ascertainment ('Hot Pursuit') of all potential stroke admissions was carried out by trained hospital personnel.

Suspect Stroke Case Definition

In order to ascertain acute stroke admissions with the highest degree of completeness, all patients who presented to the ED with clinical signs and symptoms consistent with acute stroke onset were considered as *suspect strokes cases* and were documented in a MASCOTS Suspect Stroke Logbook. *A Suspect Stroke Case* was defined as a hospital patient ≥18 years of age that had a chief complaint and/or signs or

symptoms consistent with acute-onset stroke (or rule-out stroke) of ≤14 days duration. The stroke signs and symptoms consistent with acute-onset stroke were defined as:

- Unilateral weakness
- Unilateral numbness
- Speech abnormality
- Visual disturbance
- Monocular blindness
- Dizziness/Vertigo
- Ataxia
- Acute onset inability to walk
- Altered level of consciousness

Definitive Acute Stroke Case Definition

Subjects listed on the Suspect Stroke Logbook then had to meet one of the following acute stroke subtype definitions to be considered an acute stroke admission and be assigned a study ID. The definitive acute stroke subtype definition was derived by the CDC based on previous work [58]. These definitions were used by all CDC Coverdell sites (i.e. OH, MA, MI, GA).

Coverdell Definitions of Definitive Acute Stroke (Stroke Subtypes)

The definitions of stroke subtypes are:

1. *Ischemic Stroke:* A relatively rapid onset of focal neurological deficit with signs or symptoms persisting longer than 24 hours and not attributable to another disease process. Patients who, greater than 24 hours after the onset of stroke, have only persistent sensory symptoms with minimal sensory signs or mild impairment of dexterity with normal muscle strength are included. Initial CT/MRI may show evidence of acute ischemic stroke or no evidence of stroke. When CT/MRI shows an area consistent with intracerebral hemorrhage, this may be seen only in cases with a hemorrhagic transformation of a cerebral infarct.
2. *ICH*: Non-traumatic abrupt onset of severe headache, altered level of consciousness and/or focal neurologic deficit that is associated with a focal collection of blood within the brain parenchyma on CT or at autopsy and is not due to trauma or hemorrhagic conversion of a cerebral infarction. Cases of intraventricular hemorrhage without ICH or SAH will be classified as ICH unless angiogram demonstrates an aneurysm.
3. *SAH:* Non-traumatic abrupt onset of severe headache or altered level of consciousness that is associated with blood in the subarachnoid space on CT or at autopsy, or a clinical history and exam consistent with SAH (sudden onset of severe headache or altered level of consciousness) with xanthochromia and many red blood cells in the cerebrospinal fluid. Cases that have both ICH and SAH are classified as SAH if an aneurysmal source of bleeding is documented or if the

study investigator suspects a subarachnoid origin of the bleeding. Cases are classified as ICH if a parenchymal source of bleeding seems most likely.

4. *Stroke of Uncertain Type:* Relatively rapid onset of a major focal neurological deficit that persists more than 24 hours or is fatal and cannot be attributed to another cause. This category is used when radiographic or pathologic information is insufficient to distinguish among cerebral infarction, ICH, and SAH.
5. *Transient Ischemic Attack:* Patients with acute neurologic signs and symptoms that last less than 24 hours. Patients with transient symptoms that are associated with an appropriate lesion on CT or MR imaging will be included as a TIA but not as a case of cerebral infarction. Exclude patient if symptoms no longer exists at presentation to the ED.

2.1.4 Data Collection

A standardized data collection instrument was developed that contained 87 questions organized around the following topic areas. A copy of the data elements and definitions of the instrument was included in Appendix C.

*Demographics
* EMS (emergency medical service)
* ED arrival & evaluation
* Initial imaging
* Stroke onset time
* t-PA treatment
* In-hospital diagnosis, procedures and treatment
* Prior medical history
* Discharge status
* Secondary prevention

At each hospital, a clinical data coordinator or stroke research nurse conducted active case ascertainment. Case ascertainment was conducted on a daily basis in larger hospitals (those with an average of one stroke discharge per day) and was conducted approximately 2-3 times a week at smaller hospitals. In order to ensure the accuracy and uniformity of data collection methods, the data coordinators attended an all day training session where the detailed study protocol was reviewed prior to the onset of data collection. The main sources used to identify suspect stroke cases included manual review of ED logs, ward logs, ICU logs and neurology consults.

2.1.5 MASCOTS Hospital Survey

Prior to the start of Phase II, a survey of the 16 participating hospitals was conducted to collect hospital-level information relevant to acute stroke care. A copy of the questionnaire is included in appendix D. The instrument collected information on the presence of an acute stroke team and the availability of stroke specialists (including Neurologists, Neurosurgeons, Vascular Surgeons, Radiologists/Neuroradiologists or Critical Care Physicians). The availability of written guidelines for the emergency treatment of stroke, of the in-hospital management of stroke (e.g., critical pathways, clinical pathways), and a written IV t-PA stroke protocol were assessed. Access to diagnostic technology (CT scan and MR Imaging) on hospital grounds, IV t-PA availability for the treatment of acute ischemic stroke and in-hospital rehabilitation therapy services were evaluated. Information about hospitals involved in stroke quality improvement programs, and the presence of a database or registry for tracking acute stroke patients was also documented.

2.1.6 Data Entry and Submission

Data was collected through a combination of real time data acquisition when the acute stroke patient was first identified, and retrospective data acquisition by abstraction of medical charts after patient was discharged. Data was entered either into hard copy form or Pocket PC (PDA) devices. Four of the 16 sites used PDAs to collect and submit data. All the data was submitted to MASCOTS central database electronically and then evaluated by MASCOTS data management group before all the submitted data was merged into one final data file.

2.1.7 Quality Control of the Data

The accuracy and completeness of the submitted data was checked regularly by the data management group at MSU. Data errors including logic checks and missing data were summarized in QA reports that were provided to the data coordinators. The QA reports represented a continuous iterative process.

2.2 Thesis study

2.2.1 Defining eligible patients

Eligible patients for IV tPA treatment were identified prospectively based on active case ascertainment strategies outlined above. All acute stroke patients seen in the Emergency Department (ED) within 3 hours of stroke onset, who had no evidence of hemorrhage on initial CT scan, were potentially eligible for IV tPA treatment. We excluded cases with physician-documented reasons for non-treatment with IV tPA.

2.2.2 Definition of outcome variables

The primary outcome was defined as the proportion of patients who received IV tPA. Safety was measured by the occurrence of ICH within 36 hours after tPA treatment.

2.2.3 Definition of explanatory variables

Demographic characteristics of stroke patients were grouped into categorical variables. Age was classified by decade and race was categorized into three groups (White, black and other). Insurance status was classified as Medicare (including Medicare plus any other type of insurance), Medicaid (including Medicaid plus any other type of insurance), Self-pay only and Private insurance only.

Place of residence was categorized as nursing home and elsewhere. ED arrival mode was categorized as by ambulance/air (EMS) and other modes (by car or other transportations). Initial brain Computerized Tomography (CT) results were categorized as normal, old infarct, acute infarct and other (including SAH, ICH, and other brain CT results). Functional status was estimated at pre-stroke and discharge and was categorized as able to ambulance independently, able to ambulate with assistance, unable to ambulate, and unknown. Stroke onset to ED arrival time (i.e. duration) was further classified as less than 1 hour, 1 to 2 hours, and 2 to 3 hours. The day of ED arrival was categorized as weekday or weekend/holidays and the ED arrival time was categorized into three time groups: 6:00-17:59, 18:00-23:59, and 0:00-6:00.

Processes of care including the proportion of acute stroke patients that met the NINDS recommended time intervals of ED arrival to physician evaluation time (10 minutes), ED to stroke team consult time (15 minutes), ED to CT scan time (25 minutes), ED to tPA administration time (60 minutes), stroke onset to tPA administration time (< 3 hours) were evaluated. Other processes related to IV tPA administration such as proportion of acute stroke patients that had National Institute of Health Stroke Scale (NIHSS) documented, neurologist involvement rate, and stroke team consult rate among IV tPA-treated patients were assessed. TPA therapy beyond the 3 hour window and tPA use in patients older than 85 was considered as protocol violations.

The safety of IV tPA use in MASCOTS was assessed by comparing the ICH rate and mortality rate after treatment with previous tPA clinical experience studies.

Modified Rankin Scale (mRS) at discharge was documented as 0-1, 2-3, 4-5, and 6 (death). Length of hospital stay was categorized as < 3 days, 3-6 days, 6-9 days and >

10 days. Discharge destination was categorized as home, acute rehabilitation service, nursing home, or elsewhere (such as other short term general hospital, etc.).

2.2.4 Statistical Analysis

For descriptive analysis, categorical data are presented as percent while continuous data are presented as mean with standard deviation (SD) or median with inter-quartile range (IQR). The t-test was used to test the differences in continuous variables, and X^2 test or Fisher exact test was used to compare proportions. SAS 8.2 statistical analysis programs were used to conduct all analysis.

Descriptive analysis was used to identify the difference between patients with stroke onset time known and those with onset time unknown. Age group distribution, gender, race, health insurance, place of residence, EMS arrival mode and stroke team consult were described as percentage and compared using X^2 test or Fisher's exact test, p-values were presented.

In order to investigate what demographic or clinical factors were associated with the use of IV tPA therapy among eligible patients, univariate logistic regression analysis was conducted followed by a multiple logistic regression analysis. Age, gender, race, health insurance represent basic characteristics of the patient population, and thus were considered as a priority confounding variables and included in the model regardless of significance. Other potential independent variables in the full model were selected on the basis of the strength of their univariate associations with IV tPA therapy. Only the variables with a significance level ≤ 0.3 in univariate logistic regression analysis were included in the multivariate analysis. Variables that were not statistically significant (i.e. $p>0.05$) in the multivariate model were excluded in a hierarchical backward elimination.

Adjusted odds ratios and 95% confidence intervals (CI) for all variables in the final model were reported. Homer and Lemeshow test was used to test the goodness-of – fitness of the final model.

Protocol violations and the process of care among IV tPA-treated patients were assessed by descriptive analysis.

Outcome measurements including in-hospital mortality, length of hospital stay, modified Rankin Scale, functional status at discharge, and percent discharged to home were compared between those who received IV tPA and those who did not among eligible patients. Proportion and p-value are presented.

CHAPTER 3

RESULTS

Of the original 16 hospitals selected to participate in MASCOTS, one closed down during early part of the study. A total of 2566 acute stroke patients were admitted to the 15 remaining MASCOTS hospitals during the 6-month period from May 2002 to November 2002.

3.1 Defining patients potentially eligible for tPA therapy

As described in Chapter 2, patients eligible for tPA therapy were defined using the following process as outlined in Figure 3.1.

Of the total of 2566 acute stroke patients included in MASCOTS, 469 (18.3%) had hemorrhagic signs on their initial CT image and were excluded from consideration. An additional 793 patients (30.9%) were excluded because their stroke onset times were unknown. Among the remaining 1304 patients that had onset time recorded, only 453 (34.7%) arrived to the ED within three hours of stroke onset. Based on the treating physician's evaluation for IV tPA therapy, the following subjects were regarded as ineligible and were excluded: 4 patients had no stroke symptoms on evaluation in the ED, 44 patients were judged to have undergone a significant improvement, and the stroke severity of 22 patients were considered to be too mild. Other physician documented reasons for exclusion included advanced age (n=2), CT results suggested an alternative diagnosis (n=3), uncontrolled hypertension (n=1), stroke too severe (n=4), seizure at onset (n=2), recent surgery/trauma (<15days)(n=2), recent intracranial (IC) surgery (3 months), head trauma (n=2), history of ICH or brain aneurysm or vascular malformation or brain tumor (n=4), abnormal aPTT or PT (n=6), life expectancy < 1year, and severe

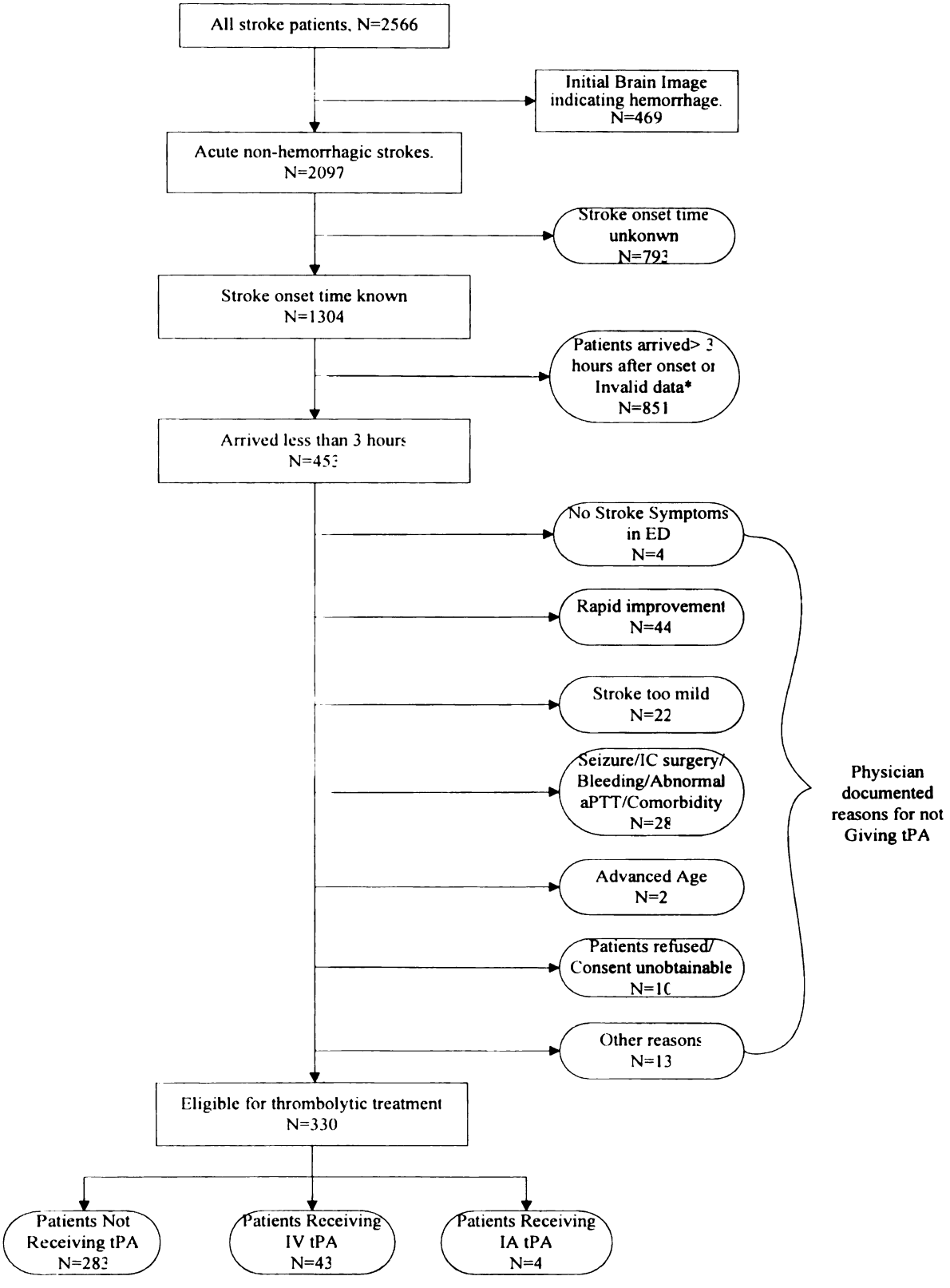


Figure 3.1 Flow Diagram Defining the Potentially Eligible Acute Stroke Patients For TPA Therapy

* Invalid data: Include patients with missing value for ED arrival time, or stroke onset time was later than the ED arrival time (8.59%).

co-morbidity (n=4). Consent was not available or the family refused treatment in 10 patients. Other miscellaneous reasons were recorded in 13 patients. Thus, of the 453 patients who arrived at ED within 3 hours of stroke onset, 123 patients (27.2%) were excluded, leaving a remaining 330 patients considered as eligible for tPA therapy. Among them, a total of 47 patients received tPA therapy (14.2%), of which 43 received IV tPA (13%) (Figure 3.1).

3.2 Characteristics of hospitals that administered tPA.

Ten hospitals administered tPA at least once during the study period while 5 did not as shown in Table 3.1. Comparison of these two groups of hospitals revealed no significant differences in any measured hospital-level characteristic, but this analysis was limited by the small sample size (Table 3.1).

In Table 3.2, the number of acute non-hemorrhagic strokes, the number and percent of patients that were eligible for tPA treatment, and the number and percent of patients that received IV tPA in each MASCOTS hospital are listed. Among acute non-hemorrhagic stroke patients, the proportion of subjects eligible for tPA treatment varied from 5% (hospital O) to 26.3% (hospital F). The percent of patients that received IV tPA treatment among these eligible patients in each hospital ranged from 0 (hospitals A, C, E, I, O) to 41.7% (hospital N). In total, 330 (15.7%) acute non-hemorrhagic stroke patients were eligible for IV tPA treatment, and 43 of these eligible patients (13.0%) received IV tPA. These 43 patients represented 2.1% of the 2097 acute non-hemorrhagic stroke patients who presented to 15 MASCOTS hospitals.

3.3 Comparison between subjects with stroke onset time known vs. unknown

As shown in Figure 3.1, nearly one third of the patients had an unclear time of stroke onset. Comparison between subjects with stroke onset time known and unknown demonstrated that patients with unknown onset time were older (mean age, 71 vs. 69, P=0.03), more likely to be female (57.5% vs. 51.5%, p<0.01), more likely to reside in a nursing home (5.4% vs. 3%, p<0.01), less likely to use EMS (36.1% vs. 47.5%, p<0.01), and less likely to have stroke team consult (32.8% vs. 52.8%, p<0.01) (Table 3.3). Health insurance has significant association with documentation of stroke onset time (chi-square statistic=11.1, df=4, p=0.03).

3.4 Comparison of demographics and clinical characteristics for patients receiving IV tPA and those not receiving IV tPA among eligible patients.

Univariate Analysis:

First, we compared the demographic and clinical characteristics of patients receiving IV tPA (n=43) to those not receiving tPA (n=283) among the 330 eligible patients using univariate logistic regression analysis. All the univariate analysis results are presented in Table 3.4 and Table 3.5.

As shown in Table 3.4, increasing age was associated with decreased use of tPA, but the trend was not statistically significant (p=0.7). Females were significantly less likely to receive tPA treatment (OR=0.4, 95%CI=0.2 – 0.9). Health insurance status was significantly associated with tPA use, when compared with patients with Medicare (with or without additional insurance), those with any other insurance plan were more likely to get tPA (Medicaid OR=3.9, 95%CI=1.4-11.3, Self pay only OR=5.2, 95%CI=1.4-19.0, and Private plan only OR=2.3, 95%CI=1.1-4.8). The association is probably was

confounded by age, however, the association between age and insurance status is further explained below. There was no significant association between residing in a nursing home and the likelihood of tPA use. The arrival mode to the Emergency Department had a strong association with IV tPA use in the univariate analysis. Those subjects who arrived by EMS, they were 6 times more likely to receive IV tPA (OR=5.6, 95% CI=2.4-12.9) (Table 3.4). When time of stroke onset was further evaluated (i.e. onset to arrival < 1 hour, 1 to 2 hours, 2 to 3 hours), those subjects who arrived during the second hour were less than half as likely to receive tPA compared with those who arrived in the first hour (OR=0.4, 95% CI=0.2-0.8), and the likelihood of receiving tPA treatment was 25 times lower for those who arrived in the third hour (OR=0.04, 95%CI=0.005-0.3). There was no significant difference between tPA use and day of arrival according to weekdays or weekends/holidays (OR=0.7, 95%CI=0.3-1.5). Patients who arrived at the ED during the night time (0:00-6:00am) tended to be less likely to receive tPA, compared to those who arrived during day time (6 am– 6 pm), but the tendency was not statistically significant (OR=0.4, 95%CI=0.04-2.7). Stroke team consultation and NIHSS score evaluation were more often conducted among tPA treated patients (OR=2.5, 95%CI=1.2-5.1 and OR=13.7, 95%CI=6.6-28.4, respectively), however both factors are more likely to represent the consequences of evaluation for tPA therapy, rather than a cause of tPA therapy, therefore neither variable were included in the multivariate modeling process. Neither image results (acute infarct or old infarct or other) or patients' pre-stroke ambulatory status had a significant association with tPA use among these eligible patients. The use of a stroke pathway also had no statistically significant association with the use of tPA.

The influence of past medical history on the probability of tPA use among acute stroke patients was also evaluated (Table 3.5). Only previous stroke /TIA history had a significant univariate association with tPA use among eligible patients (OR=0.5, 95%CI= 0.2-1.0).

Multivariate analysis:

The result of the stepwise modeling process is illustrated in Table 3.6. Three hundred and thirty patients were eligible for tPA therapy, but 7 were dropped: 4 patients received IA tPA therapy, and 3 patients whose health insurance information was missing were excluded from the analysis. Thus, a sample size of 323 was used to develop the final multiple logistic regression model. The final model included age, gender, race, ED arrival mode, and stroke onset to ED arrival time interval. The overall model global test was statistically significant ($p<0.0001$). The deviance of the final model was 193.604 with 10 degrees of freedom. The Hosmer and Lemeshow goodness-of –fit test chi-square statistic had a value of 7.8964 with 8 degrees of freedom, p-value=0.44, indicating a good model fit.

After adjusting for the other factors in the final multivariate logistic regression model as shown in Table 3.7, increasing age was still associated with a lower likelihood of receiving IV tPA treatment, but the association was not statistically significant. There was no significant difference in tPA use among different racial groups (white, black and others) (p=0.78). Females were significantly less likely to get tPA treatment than males (OR=0.4, 95%CI=0.2-0.8). Patients who arrived via EMS were 7 times more likely to receive tPA treatment compared to other transportation modes (OR=7.0, 95%CI=2.8 – 17.3). Stroke onset to ED arrival time was strongly associated with likelihood of tPA

treatment. The sooner the patient arrived at hospital the higher the likelihood of receiving tPA therapy. For patients who arrived during the second hour after stroke onset, the odds of receiving IV tPA was less than half that of those who arrived during the first hour (OR=0.4, 95%CI=0.2 – 0.8), for patients who arrived during the third hour after stroke onset (i.e. onset to ED arrival time is 2-3 hours), the odds of receiving tPA was 0.03 (OR=0.03, 95%CI=0.004 – 0.2).

Further analysis indicated that as expected insurance status was strongly associated with age (Table 3.8), 76 out of 102 patients (74.5%) less than 65 years of age had private insurance, while 198 out of 221 patients (89.6%) older than 65 had Medicare. It was therefore difficult to include both variables in the multivariate model. Thus age was retained in the multivariate logistic regression model to avoid the redundant effect of including both age and insurance. Stratified analysis showed that among those under 64 years group, there was no association between insurance type (private insurance plan vs other) and tPA use (OR=0.95, 95%CI= 0.3 – 3.3), while for those ≥ 65, the vast majority of them had Medicare (198/221), but they were less likely to receive tPA than those who had other insurance types (OR=0.28, 95%CI= 1.2 – 10.1), while the estimate was very imprecise because of the wide 95%CI.

3.5 Process of care surrounding IV tPA therapy.

The processes of care surrounding the administration of IV tPA were assessed. The NINDS recommended time intervals for tPA administration are shown in Table 3.9. The median time from ED arrival to physician evaluation was 25 minutes for all eligible patients, and only 17.8% were seen by the physician within 10 minutes of arrival (the recommended time interval). The median time from ED arrival to acute stroke team

consult was 34 minutes, and only 10.4% received a consult within 15 minutes of their arrival as recommended by the NINDS. The median time from ED arrival to CT scan was 75 minutes, and only 7% had their CT scan within the recommended 25 minutes after arrival to the ED. The median time from ED arrival to receiving tPA was 83 minutes, only 7 patients (16.3%) received tPA within 1 hour after they arrived at the ED, while the majority (n=28, 68.2%) received treatment between 1 and 2 hours after arrival at ED. The median time from stroke onset to tPA therapy was 150 minutes, most patients (n=35, 81%) received their tPA within recommended 3 hour treatment window. Six of the eight patients received their IV tPA beyond the 3-hour window and one was treated exactly at three hours after stroke onset, the remaining one didn't have a tPA administration time recorded (Table 3.9).

Among 330 eligible patients, only 51 had a baseline NIHSS score recorded, of which 25 received tPA therapy, or 25 out of 43 IV tPA treated patients (58%) had a baseline NIHSS score recorded. All of the tPA patients had a neurologist involved in their care during hospitalization. Stroke team consultation was recorded among 74% of the tPA patients.

Information on specific protocol violations was very limited in our data. There were three patients (7.0%) older than 85 who received tPA and six patients (14.0%) who received their treatment beyond the three hour time window, but none of them had complications (Table 3.9).

3.6 Complication rates after IV tPA therapy

Five of the 43 patients had complications after tPA therapy (11.6%). Intracranial hemorrhage occurred in two patients (4.6%), one of which died as a consequence. This

patient was treated at exactly 3 hours after stroke onset, and had a very serious pre-tPA NIHSS of 28. The other four tPA patients were treated between 2 to 3 hours after stroke onset.

3.7 Comparison of outcomes between patients treated with tPA and those not treated among eligible patients.

Outcome data was limited to that recorded at discharge, and information on stroke severity before treatment was incomplete because NIHSS was recorded in only 15.6% of the eligible patients. A comparison of those treated with tPA with those not treated with tPA (among eligible patients) demonstrated that tPA treated patients had generally worse short-term outcomes (Table 3.10). The in-hospital mortality rate was significantly higher among patients receiving tPA (9.3% vs. 1.4%, p=0.01). A higher proportion of patients who received tPA therapy had moderate to severe disability (Modified Rankin Scale: 4-5) at discharge compared to those that did not receive tPA (51.3% vs 20.3%, p<0.01). Functional status was also measured by assessing ambulatory status. A higher proportion of tPA treated patients were unable to ambulate at discharge, compared to untreated cases (23.7% vs 8.2%, p<0.01). The mean length of stay for tPA patients were 7.2 days compared with non-tPA patients of 4.2 days (p< 0.01). Patients who received tPA were also less likely to be discharged back to home (56.4% vs 76.7%), and were more likely to be discharged to nursing home (12.8% vs 6.8%) or acute rehabilitation services (25.6% vs 14.0%), however the association between discharge destination and tPA use was marginally statistically significant (p=0.08) (Table 3.10).

Our definition of eligible patients was first determined by the initial CT image findings, however the final stroke subtype diagnosis may be different from the initial

image results as symptoms might develop. Comparison of the final diagnosis of those who received tPA with those that did not demonstrated that all tPA patients had a final diagnosis of ischemic stroke, while only 58.3% of the non-tPA treated patients had a final diagnosis of ischemic stroke. In fact, 40.3% of non-tPA treated patients had a final diagnosis of TIA (n=114), and there were 1.4% of the patients diagnosed as hemorrhagic stroke even though their initial image results were negative for hemorrhage (n=4) (Table 3.10).

Table 3.1 Comparison of hospital characteristics between those that administered tPA and those that did not.

Variables	Hospitals administered tPA (N=10) (N, %)	Hospitals did not administer tPA (N=5) (N, %)
Stroke team available	5 (50.0)	3 (60.0)
Stroke guidelines used in ED	7(87.5)	4(80.0)
Guidelines in-hospital	6(60.0)	4(80.0)
Physician expertise availability		
Neurologist	9(90.0)	4(80.0)
Neurosurgeon	9(90.0)	4(80.0)
Vascular Surgeon	9(90.0)	4(80.0)
Radiologist	10(100.0)	5(100.0)
Critical care physician	9(90.0)	5(100.0)
CT scan availability	10(100.0)	5(100.0)
MRI availability	6(60.0)	3(80.0)
IV tPA availability	10(100.0)	5(100.0)
IV tPA protocol	9(90.0)	5(100.0)
Previous experience*	9(90.0)	4(80.0)
Full rehabilitation service**	8(80.0)	3(60.0)
Stroke registry available***	7(70.0)	2(40.0)
Hospital discharge per year, median (range)	631(383 – 879)	586(193 – 979)

* Previous experience of participation in stroke quality improvement programs.
** Full Rehabilitation Service: Speech therapy, Physical therapy, Occupational therapy, Social worker, discharge planner, Case manager nurse practitioner or clinical nurse specialist
*** Stroke database or registry in hospital.

Table 3.2 Number and percent of eligible patients and IV tPA recipients by hospitals

Hospital	Number of Acute Non-hemorrhagic Strokes(A)	Number of Eligible Patients (B) N (%)*	Number of Patients Who Received IV tPA (C) N (%)**
A	83	7(8.4)	0(0.0)
B	149	26(17.4)	5(20.8)
C	171	17(9.9)	0(0.0)
D	153	33(21.6)	3(9.1)
E	164	16(9.8)	0(0.0)
F	95	25(26.3)	5(20.0)
G	219	56(25.6)	8(14.3)
H	129	15(11.6)	1(7.7)
I	104	13(12.5)	0(0.0)
J	330	65(19.7)	11(16.9)
K	150	14(9.3)	1(7.1)
L	139	20(14.4)	1(5.0)
N	131	12(9.2)	5(41.7)
O	20	1(5.0)	0(0.0)
P	60	10(16.7)	3(30.0)
Total	2097	330(15.7)	43(13.2)

A: Excluded patients with hemorrhagic image results.
B: Defined as acute stroke patients that arrived at ED within 3 hours of stroke onset and had no physician documented reasons for non-treatment.

* Percentage (%) = (B/ A) X100%
** Percentage (%) = (C/ B) X 100%

Table 3.3 Comparison between patients with stroke onset time known and stroke onset time unknown.

Variables	Patients With Onset Time Known (N=1304) (N, %)	Patients With Onset Time Unknown (N=793) (N, %)	P value*
Age (Mean±StD)	69±14.7	71±14.7	0.03
Age (Categorical)			0.2
18-39	41(3.1)	26(3.3)	
40-49	98(7.5)	57(7.2)	
50-59	197(15.1)	99(12.5)	
60-69	253(19.4)	141(17.8)	
70-79	380(29.1)	226(28.5)	
80-89	279(21.4)	197(24.8)	
>90	56(4.3)	47(5.9)	
Gender			<0.01
Male	633(48.5)	337(42.5)	
Female	671(51.5)	456(57.5)	
Race			0.43
White	969(74.3)	606(76.4)	
Black	216(16.6)	129(16.3)	
Other	48(3.7)	20(2.5)	
UNK	71(5.4)	38(4.8)	
Health Insurance**			0.03
Medicare plus Other	810(62.5)	502(63.4)	
Medicaid plus Other	110(8.5)	93(11.7)	
Self Pay	46(3.6)	17(2.2)	
Private only	331(25.5)	180(22.7)	
Nursing home			<0.01
No	1265(97.0)	750(94.6)	
Yes	39(3.0)	43(5.4)	
EMS arrival Mode			<0.01
Other	684(52.5)	507(63.9)	
Ambulance/Air (EMS)	620(47.5)	286(36.1)	
Stroke Team Consult			<0.01
No	615(47.2)	533(67.2)	
Yes	689(52.8)	260(32.8)	

*As generated by Chi-square test.

**8 observations have missing values for health insurance.

Table 3.4 Univariate associations between demographic or clinical factors and the likelihood of IV tPA therapy among eligible patients

Variables	IV tPA Patients (N=43) (N, %)	Eligible Patients Not Receiving TPA (N=283) (N, %)	OR (95% CI)	P value*
Age (Mean±StD)	66.4±14.8	70.0±14.0		0.59
Age Group				0.70
18-49	7 (16.3)	27 (9.5)	1.00	
50-59	6 (14.0)	34 (12.0)	0.7 (0.2 – 2.3)	
60-69	8 (18.6)	61 (21.6)	0.5 (0.2 – 1.5)	
70-79	13 (30.2)	86 (30.4)	0.6 (0.2 – 1.6)	
>80	9 (20.9)	75 (26.5)	0.5 (0.2 – 1.4)	
Gender				0.02
Male	28 (65.1)	128 (45.2)	1.00	
Female	15 (34.9)	155 (54.8)	0.4 (0.2 - 0.9)	
Race				0.61
White	33 (76.7)	221 (78.1)	1.00	
Black	5 (11.6)	41 (14.5)	0.8 (0.3 - 2.2)	
Other	5 (11.6)	21 (7.4)	1.6 (0.6 - 4.5)	
Health Insurance**				<0.01
Medicare plus Other	18 (41.9)	188 (67.1)	1.00	
Medicaid plus Other	6 (13.9)	16 (5.7)	3.9 (1.4 – 11.3)	
Self Pay	4 (9.3)	8 (2.9)	5.2 (1.4 – 19.0)	
Private only	15 (34.9)	68 (24.3)	2.3 (1.1 – 4.8)	
Nursing Home				0.95
No	42 (13.2)	276 (86.8)	1.00	
Yes	1 (12.5)	7 (87.5)	0.9 (0.1 – 7.8)	
ED arrival Mode				<0.01
Other	7 (16.3)	147 (51.9)	1.00	
Ambulance/Air (EMS)	36 (83.7)	136 (48.1)	5.6 (2.4 – 12.9)	

(To be continued)

* As generated by univariate logistic analysis.

* *3 observations have missing value at Health insurance.

Table 3.4 Univariate associations between demographic or clinical factors and the likelihood of IV tPA therapy among eligible patients (Continued)

Variables	IV tPA Patients (N=43) (N, %)	Eligible Patients Not Receiving TPA (N=283) (N, %)	OR (95% CI)	P value*
Onset to ED Arrival time				<0.01
< 1hour	26 (60.5)	78 (27.6)	1.0	
1 to 2 hours	16 (37.2)	119 (42.1)	0.4(0.2 – 0.8)	
2 to 3 hours	1 (2.33)	86 (30.4)	0.04 (0.005 – 0.3)	
ED Arrival date				0.33
Weekday	34(79.1)	204(72.1)	1.0	
Weekend/Holiday	9 (20.9)	79 (27.9)	0.7 (0.3 –1.5)	
ED Arrival time				0.19
06:00-17:59	23 (53.5)	168(59.4)	1.0	
18:00- 23:59	19 (44.2)	94 (33.2)	1.5 (0.8- 2.9)	
00:00- 06:00	1 (2.3)	21 (7.4)	0.4 (0.04 - 2.7)	
Stroke team Consult				0.01
No	11 (25.6)	130 (45.9)	1.00	
Yes	32 (74.4)	153 (54.1)	2.5 (1.2 – 5.1)	
NIHSS Documented				<0.01
No	18 (41.9)	257 (90.8)	1.00	
Yes	25 (58.1)	26 (9.2)	13.7 (6.6 – 28.4)	
Image results				0.61
Normal	19 (44.2)	99 (35.0)	1.00	
Old Infarct	11 (25.6)	76 (26.9)	0.8 (0.3 – 1.7)	
Acute Infarct	5 (11.6)	33 (11.7)	0.8 (0.3 – 2.3)	
Other	8 (18.6)	75 (26.5)	0.6(0.2 – 1.3)	
Pre-stroke Status**				0.74
Ambulate independently	40 (95.2)	255 (93.4)	1.0	
Ambulate with Assist	1 (2.4)	13 (4.8)	0.5 (0.1 – 3.9)	
Not Ambulate	1 (2.4)	5 (1.8)	1.3 (0.2 – 11.2)	
Stroke Pathway				0.28
No	27 (62.8)	201 (71.0)	1.0	
Yes	16 (37.2)	82 (29.0)	1.5 (0.7 – 2.8)	

* As generated by univariate logistic analysis.

* 11 observations have missing value in Pre-stroke status.

Table 3.5. Univariate Associations between past medical history and likelihood of tPA therapy among eligible patients

Variables	tPA Patients (N=43) (N, %)	Eligible Patients Not Receiving TPA (N=283)(N, %)	OR (95%CI)	P value *
Stroke/Transient ischemic attack (TIA)/ Vertebrobasilar territory ischemia (VBI)				0.05
Absent	32 (74.4)	168 (59.4)	1.0	
Present	11 (25.6)	115 (40.6)	0.5 (0.2 – 1.0)	
Myocardial Infarction (MI)				0.62
Absent	37 (86.1)	235 (83.0)	1.0	
Present	6 (13.9)	48 (17.0)	0.8 (0.3 – 2.0)	
Coronary Heart Disease (CHD)				0.38
Absent	32 (74.4)	192 (67.8)	1.0	
Present	11 (25.6)	91 (32.2)	0.7 (0.4 – 1.5)	
Atrial Fibrillation (AF)				0.61
Absent	38 (88.4)	242 (85.5)	0.8 (0.3 – 2.1)	
Present	5 (11.6)	41 (14.5)		
Congestive Heart Failure (CHF)				0.28
Absent	39 (90.7)	240 (84.8)	1.0	
Present	4 (9.3)	43 (15.2)	0.6 (0.2 – 1.7)	
Valve Prothesis				0.95
Absent	42 (97.7)	276 (97.5)	1.0	
Present	1 (2.3)	7 (2.5)	0.9 (0.1 – 7.8)	
Hypertension (HTN)				0.56
Absent	15 (34.9)	86 (30.4)	1.0	
Present	28 (65.1)	197 (69.6)	0.8 (0.4 – 1.6)	
Dyslipedemia				0.29
Absent	31 (72.1)	181 (64.0)	1.0	
Present	12 (27.9)	102 (36.0)	0.7 (0.3 – 1.4)	
Diabetes Mellitus (DM)				0.40
Absent	34 (79.1)	207 (73.1)	1.0	
Present	9 (20.9)	76 (26.9)	0.7 (0.3 – 1.6)	

* As generated by univariate logistic analysis.

For those variables have P<0.3 are included in the following multiple logistic regression model selection.

Table 3.6. Model Selection for tPA therapy among 323 patients: Hierarchical Backward Elimination Approach.

	-2lnL*	DF**	Δ Deviance***	Δ DF	P
(1) No covariates	253.418				
(2) Full model (age, gender, race, EMS, stroke pathway, Stroke/TIA/VBI history, Congestive Heart Failure history, Dyslipidemia history, ED arrival time, Onset to ED arrival time interval)	186.480	16			
(3) Reduced model- Congestive Heart Failure history	187.190	15	0.71	1	0.4
(4) Reduced model- Dyslipidemia history	187.435	14	0.245	1	0.6
(5) Reduced model- Dyslipidemia history	189.408	12	1.973	1	0.4
(6) Reduced model- stroke pathway	190.586	11	1.178	2	0.6
(7) Reduced model- Stroke/TIA/VBI history	193.604	10	3.018	1	0.08
Final Model (age, gender, race, EMS, Onset to ED arrival time interval)	193.604	10			

Full model includes age, gender, race, EMS, stroke pathway, Stroke/TIA/VBI history, Congestive Heart Failure history, Dyslipidemia history, ED arrival time, Onset to ED arrival time interval

Final model includes 5 variables: Age; gender; race; EMS mode; Onset to ED arrival time interval

*-2 Log Likelihood
** Degrees of freedom
*** Δ Deviance=the difference of –2 log likelihood between two consecutive models.

Table 3.7 Final multiple logistic regression model relating demographic and clinical characteristics to the likelihood of tPA therapy in eligible ischemic stroke patients (N=323)

Variables	N (%)	OR	95%CI	P value*
Age Group				0.5
18-49	32(9.9)	1.0		
50-59	40(12.4)	0.4	0.1-1.7	
60-69	68(21.0)	0.4	0.1-1.3	
70-79	99(30.7)	0.3	0.1-1.1	
>80	84(26.0)	0.4	0.1-1.2	
Gender				
Male	154(47.7)	1.0		
Female	169(52.3)	0.4	0.2 – 0.8	<0.01
Race				0.78
White	252(78.0)	1.0		
Black	45(13.9)	0.8	0.2 – 2.5	
Other	26(8.0)	1.3	0.4 – 4.3	
EMS				<0.01
Other	152(47.1)	1.0		
Ambulance/Air (EMS)	171(52.9)	7.0	2.8 – 17.3	
Stroke Onset to ED Arrival time				<0.01
< 1hour	104(32.2)	1.0		
1 to <2 hours	135(41.8)	0.4	0.2 – 0.8	
2 to <3 hours	84(26.0)	0.03	0.004 – 0.2	

*Calculated from likelihood ratio chi-square test

Table 3.8 Relationship between age and insurance type

Age group	Insurance type				Total
	1) Medicare	2) Medicaid	3) Private	4) Self-pay	
18-64	8(7.8)	8(7.8)	76(74.5)	10(9.8)	102(31.6)
>65	198(89.6)	14(6.3)	7(3.2)	2(0.9)	221(68.4)
Total	206	22	83	12	323

Chi-square test: X^2 =226.4717 with Degrees of freedom (df) of 3, thus P-value<0.0001

Age group=18-64:

Insurance Type	TPA therapy		Total
	Yes	No	
Private	14(73.7)	62(74.7)	76
Else	5(26.3)	21(25.3)	26
Total	19	83	102

Fisher's exact:
Two-sided Probability: P-value=1.0
OR: 0.95, 95%CI: 0.3-3.3

Age group=>65:

Insurance Type	TPA therapy		Total
	Yes	No	
Medicare	18(75.0)	180(91.4)	198
Else	6(25.0)	17(8.6))	23
Total	24	197	221

Fisher's exact:
Two-sided Probability: P-value=0.02
OR: 0.28, 95%CI 1.2-10.1

Table 3.9 Processes of Care related to IV tPA administration and Identified Protocol Violations:

Variables	Number Of Patients	%
NINDS recommended time intervals		
ED arrival to physician evaluation time<10 minutes[1]	58	17.8
ED arrival to stroke team consult time<15 minutes[1]	34	10.4
ED arrival to CT scan time<25 minutes[1]	23	7.1
Percent got tPA < 1 hour after ED arrival[2]	7	16.3
Percent got tPA < 3 hour after Stroke onset[2]	35	81.4
Other Processes related to IV tPA administration		
NIHSS documented[2]	25	58.1
Neurologist involvement [2]	43	100.0
Stroke team consult[2]	32	74.4
Protocol violations		
Treated >3hr[2]	6	14.0
Age>85 year[2]	3	7.0

1: Percentage was determined based on all eligible patients (N=326)
2: Percentage was determined based on IV tPA treated patients (N=43)

Table 3.10 Comparison of Outcomes between patients treated with tPA and those not treated among eligible patients.

Variables	IV tPA Patients (N=43)	Eligible Patients Not Treated With tPA (N=283)	P
In-hospital Mortality			
Alive	39(90.7)	279(98.6)	0.01
Die in hospital	4(9.3)	4 (1.4)	
Modified Rankin Scale at discharge+[&]			<0.01
0-1	14(35.9)	156 (58.7)	
2-3	5(12.8)	56 (21.1)	
4-5	20(51.3)	54 (20.3)	
Functional Status at discharge[#&]			<0.01
Able to Ambulate independently	16(42.1)	198(73.9)	
Ambulate with assistant from others	13(34.2)	48(17.9)	
Not able to ambulate	9(23.7)	22(8.2)	
Length of Stay* (mean ± Std)	7.2 ± 5.8	4.2 ± 3.2	<0.01
< 3 days	5(11.6)	90(32.7)	
3 - 6 days	15(34.9)	123(44.7)	
6 - 10 days	16(37.2)	46(16.7)	
>10 days	7(16.3)	16(5.8)	
Discharge Destinations[&]			0.08
Home	22(56.4)	214(76.7)	
Nursing Home	5(12.8)	19(6.8)	
Acute Rehabilitation service	10(25.6)	39(14.0)	
Others	2(5.1)	7(2.5)	
Final Coverdell Diagnosis			
Ischemic Stroke	43 (100.0)	155(54.8)	
SAH		1 (0.3)	
TIA		114 (40.3)	
Hemorragic of uncertain type		3 (1.1)	
Ischemic stroke of uncertain type		10(3.5)	

* 8 observations have missing value in length of stay.

\+ 13 observations have missing value in Modified Rankin Scale.

\# 12 observations have missing value in functional status.

[&] Exclude 8 patients died in the hospital.

CHAPTER 4

DISCUSSION

In this study, 13% of the eligible patients (N=43) received IV tPA treatment. However, these 43 tPA-treated patients represented only 2.1% of all the non-hemorrhagic strokes (N=2097) presenting to the 15 MASCOTS hospitals. Previous studies related to the IV tPA use in clinical practice reported that the percent of IV tPA treated patients ranged from as low as 1.8% among stroke patients with discharge ICD-9 codes of 434 and 436 in Cleveland Experience Study to 22% among presumed acute stroke patients in a prospective open-label single center study in Cologne, Germany [39, 41]. Some prospectively designed studies have reported a tPA treatment rate of 6% to 9% among all ischemic strokes [47, 48, 59]. The percent of IV tPA treated patients in our study is relatively low compared to a similar designed study conducted in Berlin in 1998 which reported that 47% of potentially eligible patients (i.e. admitted within 3 hour from symptom onset) were treated with IV tPA [60]. It's not clear why there is such a big difference but it could be due to the difference in clinical settings and triage structures. In our study, a wide range of hospitals were included from large, university medical centers to small community hospitals, thus reflecting the real life tPA use across the Michigan.

4.1 TPA use at the hospital level

Hospital-level information potentially relevant to tPA administration collected as part of the MASCOTS hospital survey was limited. Hospitals administering tPA had similar facilities to those that did not use tPA. There was no significant difference according to their geography, sampling strata or peer grouping. All hospitals had CT scan facilities available and IV tPA was available for treatment of acute ischemic stroke

patients. There was no difference in the use of stroke guidelines, acute stroke teams or the type of physician expertise availability between the hospitals that did and did not use tPA. Hospitals that administered tPA had more previous experience in participating in stroke research projects and in maintaining their own in-hospital stroke registry compared to the other hospitals (70% vs 40%). These results reflect that tPA treatment is generally given at larger and more experienced hospitals, although this was not clearly reflected in the available hospital-level data.

4.2 Reasons for patient ineligibility for tPA treatment:

The most common reasons that subjects were ineligible for tPA use were lack of documentation of stroke onset time and delayed presentation. Nearly 40% of patients (793/2097) had no stroke onset time documented, and among patients that had stroke onset time documented, only 35% of the patients (453/1304) arrived to the ED within 3 hours of stroke onset. Among the patients who arrived at the ED within 3 hours of their stroke onset, 27% (123/453) had physician documented reasons for non-use of tPA therapy, which include contraindications (such as rapid improvement, mild strokes, uncontrolled hypertension, risk of bleeding) as well as other reasons documented by the physician (such as patient or family refused, consent not obtainable). Of the remaining eligible patients (N=330), 86% of them (283/330) didn't receive IV tPA treatment and had no specific reasons documented.

4.2.1 Lack of documentation of stroke onset:

Our study showed that a great proportion of patients (40%) did not have their stroke onset time documented. Subjects without a documented onset time were more

likely to be older, female, and residing in nursing home. Being female and residing in nursing home is likely to be confounded by age, because females tend to live longer, and people who resided in nursing home were older.

The lack of documentation of stroke onset time may be attributed in part to the lack of knowledge of stroke warning signs and symptoms. In a population-based telephone survey conducted by Pancioli et al [61], stroke warning signs and symptoms as defined by NINDS were used to assess the knowledge of stroke warning signs in a population in the Greater Cincinnati, Ohio with similar demographic characteristics (e.g. age, race, sex, and economic status) to the overall United State population. Warning signs of stroke include sudden weakness or numbness of the face, arm, or leg; sudden dimness or loss of vision; sudden difficulty speaking or understanding speech; sudden severe headache with no known cause; and unexplained dizziness, unsteadiness, or sudden falls. Only 57% of the respondents correctly listed at least one stroke warning sign, respondents older than 75 were less likely to know the stroke warning signs, compared with those younger than 75 (OR=0.6, 95%CI= 0.5-0.8). In their final multivariate logistic regression model, younger age, female sex, higher level of education, previous smoking, and a history of previous stroke or TIA were significantly associated with knowledge of stroke warning signs. A similar population-based statewide survey of knowledge of stroke risk factors and warning signs among Michigan adults by Reeves et al [62] found that almost one in three respondents were not aware of any stroke warning signs. Other studies have also demonstrated that many patients have little knowledge about stroke. Kothari et al found that among patients admitted from the ED, that almost 40% did not know a single sign or symptom of stroke. This study also found that older patients (> 65

years) were less likely to know signs or symptoms of stroke compared to those aged < 65 years of age. Only 49% of the patients realized that a stroke was due to an injury to the brain. Patients who were able to identify signs and symptoms of a stroke were more likely to recognize when they were having a stroke at onset [63]. Another study showed that 22% of patients believed that stroke and heart attack are the same [64]. Other possible reasons for lack of documentation of stroke onset may be attributed to no witness when the stroke occurs or poor documentation of medical charts by medical service providers.

4.2.2 Delayed presentation:

Presentation to the ED greater than three hours after stroke onset was the major reason that patients were ineligible for tPA treatment. Sixty-five percent of those with known onset time arrived >3 hours after stroke onset. The lack of knowledge of stroke signs and symptoms is thought to be one of the major reasons for delay in seeking medical care [43].

Lack of knowledge of stroke could also result in inappropriate interpretation of the severity of stroke symptoms and signs, and thus cause pre-hospital delay. A study conducted by Williams et al has found that many of the patients presenting beyond 3 hours after stroke onset thought that their symptoms were not serious, and thus were reluctant to call an ambulance while resulted in delayed presentation [65]. Other studies have reported that there is an association between stroke severity and presentation time where early arrival patients have more severe strokes than late arrivals [66-68]. Patients with near normal function tend to not call the ambulance, thus arrive late; while patients who arrived by ambulance had more severe functional limitations, and thus are more

likely to arrive earlier [66-68]. The Copenhagen Stroke Study conducted in 1996 found that stroke severity was independently associated with early admission, a 10-point increase in the Scandinavian Stroke Scale (SSS) on admission (less severe stroke) increased the relative risk of delayed admission by odds of 1.25(95% CI=1.14-1.36) [66].

Emergency Medical Service (EMS) played an important role in facilitating access to health care and tPA treatment among acute stroke patients. Our study showed that patients who knew their stroke onset time (i.e. onset time was recorded as specific or estimated) were more likely to call an ambulance (47.5% vs 36.1%, $p<0.01$). Among eligible patients who arrived with 3 hours of stroke onset, our results demonstrated that those arrived via EMS were still 7 times more likely to receiving tPA therapy than those arrived via non-EMS transportation (i.e. car, walk-in, bus etc.). Previous studies have shown that travel time to the hospital was just a small proportion of the total pre-hospital delay [66]. The reduction in pre-hospital and in-hospital delays due to EMS use must therefore be attributed to other reasons. In the Delay in Accessing Stroke Healthcare (DASH) study, they assessed the determinants of pre-hospital delay for care among ischemic stroke patients and found that EMS use was associated with decreased pre-hospital and in-hospital delay. Recognition of symptoms by a witness other than patient himself was associated with use of EMS, and thus resulted in faster arrival to the ED [69]. Similar associations between ED arrival mode and early presentation and evaluation among stroke patients have been reported in other studies [65, 70]. Thus, EMS use maybe a surrogate or proxy for patients that have a known onset time and/or greater stroke severity.

In summary, significant efforts are needed to improve public knowledge of signs and symptoms of stroke. When stroke signs and symptoms are identified, the patient or the witness should activate the 911 system immediately. Older population has greater risk of stroke but who appear to be the least informed group. However, stroke education should target everyone in the community regardless of age, because stroke patients often have impaired ability to communicate or are unable to recognize their symptoms. Therefore, community education is important so that everyone can help facilitate the rapid identification and transport of the potential stroke patients to the hospital [61, 71].

4.2.3 Documented reasons for non-treatment

There were 123 patients who arrived at ED within 3-hour treatment window but had physician documented reasons for not giving IV tPA. Similar to the other studies [47, 72], the most common reasons for not giving tPA at this point were that stroke symptoms improved rapidly (44/123, 35.8%) or the stroke was too mild to receive IV tPA therapy (22/123, 17.9%).

4.2.4 In-hospital delay and processes of care

Of the 283 eligible patients that did not receive IV tPA, no specific reasons for withholding treatment was recorded. We can therefore only hypothesize that a combination of in-hospital delays, lack of appropriate health care facilities, and individual hospital or physician preferences against the use of tPA attributed to this non-use. Even if patients could recognize stroke symptoms and arrive at hospital within 3 hours of stroke onset, they still need enough time to undergo evaluation, have a CT scan performed and interpreted, and wait for IV tPA administration and preparation.

Our data demonstrated that the sooner the patients arrived to the ED, the higher the likelihood they would receive tPA treatment. The NINDS has recommended the following time frames as goals for acute stroke management: ED arrival to physician evaluation < 10 minutes; ED arrival to stroke team consult < 15 minutes; ED arrival to CT scan < 25 minutes; ED arrival to tPA initiation < 1 hour [73]. In our study, only 18% (58/326) of the eligible patients (i.e. those arrived at ED within 3 hours of their stroke onset and no physician documented reasons for non-use) received physician evaluation < 10 minutes after they arrived at ED (median=25minutes), only 10.4% (34/326) of the eligible patients had acute stroke team consultation < 15 minutes of their ED arrival (median=34 minutes), and only 7% (23/326) of the eligible patients received CT scan < 25 minutes after they arrived at ED (median=75 minutes). The median time interval from ED arrival to tPA administration was 83 minutes, only 7 patients (16.3%) received tPA within 1 hour after they arrived at ED as recommended by NINDS. The majority of patients (n=28, 68.2%) received tPA therapy during the second hour after arriving at ED. A prospective study conducted at the 10 hospitals of New Jersey showed that waiting time for initial physician evaluation was significantly shorter for those arrived by ambulance [74]. A retrospective study of documenting in-hospital time intervals by Kothari et al in 4 hospitals of Ohio [75] found that the median time from ED arrival to physician evaluation was 18 minutes, only 37% of patients were evaluated within 10 minutes. They also found that the median time from ED arrival to CT was 72 minutes, only 17% of patients had a CT scan within 25 minutes of ED arrival, and even among patients presenting within 3 hours of symptom onset, the median time to CT was 45 minutes. The relative longer in-hospital delays in our study may due to a wider range of

hospitals, including some small community hospitals and hospitals with less experience on acute stroke management, are included in our study. The four hospitals in Ohio were actively involved in acute thrombolytic stroke trials, thus had more experience and/or infrastructure facilities treating acute stroke patients [75]. In a survey conducted among neurologists in 16 cities from 1997 to 1998, only half of the survey respondents thought their institutions met all the NINDS-recommended time targets. The neurologist considered that "door to doctor" within 10 minutes and " door to neurological expertise " within 15 minutes were the most difficult time targets to meet, suggesting the need to improve the infrastructure to rapidly assess potential thrombolysis candidates [76]. Proper infrastructures and the hospital facilities could potentially facilitate more and earlier tPA therapy among eligible patients. The American Stroke Association recommended that infrastructure for implementing tPA therapy including establishing an acute stroke care team, initiating physician and staff training in acute stroke care, establishing links to the EMS system, and ensuring that CT scan are available at all time need to be implemented [77, 78].

4.2.5 Other Miscellaneous Reasons for Non-use of tPA

None of the previous comorbidities (i.e. previous history of stroke, hypertension, myocardial infarction, atrial fibrillation, congestive heart failure, diabetes) had any significant influence on the likelihood of receiving tPA therapy. In a subgroup analysis identifying variables that might predict outcome or response to tPA therapy in the NINDS tPA Stroke Trial, investigators found that no pre-treatment information (variables that might influence outcome after stroke or might influence clinical response to tPA, including patients' medical history) significantly affected patients' response to tPA as

long as the patients were selected according to the guidelines [79, 80]. Thus, evidence from both our study (observational in nature) and the subgroup analysis from NINDS trial demonstrated that sub selection of patients is not supported. However, sub selection of eligible patients for tPA therapy beyond the treatment protocol is reported in a study based on the Cleveland Community Experience. Researchers found that the two most common reasons that tPA was not given in otherwise eligible patients were older age (defined as >77 years) and a history of dementia [72].

Physicians' reluctance to use IV tPA therapy may be another reason that eligible patients didn't received treatment. Fear about hemorrhagic complications and the uncertainty about tPA efficacy among neurologists have been reported as the major reason limiting the widespread use of tPA [55]. Results from the Brain Matters Stroke Mangement Survey conducted in 1997 in 16 cities of United States reported that 62% neurologists were "very concerned", and 37% were "somewhat concerned" with regard to ICH after tPA therapy. Neurologists who had used tPA were more convinced by its efficacy and less concerned about ICH than those who had no experience of administering tPA [76].

4.2.6 Gender disparities in tPA treatment

In the current study, women were less likely to record their stroke onset time (57.5% vs 42.5%, $p<0.01$). Even when women arrived within three hours of stroke onset, after adjusting for age, EMS mode, and stroke onset to ED arrival time, their odds of getting tPA treatment was 40% that of men (OR=0.4, 95%CI= 0.2-0.8). This finding has not been reported in previous studies of tPA use. Similar treatment disparities have been reported in the treatment of cardiovascular disease. Studies have demonstrated that

women undergo far fewer coronary revascularization procedures relative to men with comparable disease [81, 82]. In a study evaluating critical factors determining access to acute stroke care in Houston, TX, they found that women got to the hospital significantly later than men (i.e. median time interval: 895 vs 648 minutes), and ED physicians saw men significantly faster than women (i.e. 29 vs 21 minutes) when other related factors including stroke type and severity were controlled for [83]. These results suggested that prompt attention and interventions specific to women are necessary to narrow this gender disparity.

4.3 Complications of tPA therapy

Safety is always a major concern for tPA use in clinical practice. In the NINDS trial, symptomatic ICH occurred in 6.4% of the tPA treated patients compared with 0.64% in the placebo group [20]. Subsequent studies showed that protocol violations, severe stroke (NIHSS>20), and early ischemic signs on pretreatment CT scans were predictors of serious complications of ICH [51, 84]. The symptomatic ICH rate in our study was 4.1% (2/43) which was similar to the other studies that reported ICH rate of between 3 to 6%. The Cleveland experience study reported the highest ICH rate at 16% [38-41, 44, 59]. As seen in the summary table of ICH rates after IV tPA (Table 4.1), the symptomatic ICH rate declined over time. This trend was also reported in a study in four years experience from Houston [59]. The overall complication rate in our study was 11.6% (5/43), with one patient had a fatal ICH.

In order to minimize the risk of tPA therapy, close attention to the presence of contraindications needs to occur, including prompt accurate interpretation of pretreatment CT scan, clear documentation of stroke severity using the NIHSS score, consistent

clinical evaluation of patients, and stringent attention to treatment protocols. Physicians that unfamiliar with acute stroke management and treatment protocol may inappropriately use tPA in high risk patients, resulting in increased rates of ICH. Early infarction on CT is often missed even by experienced doctors [85], and the NIHSS was only evaluated in a small proportion of patients in our study. Survey about physicians' knowledge of the tPA therapy showed that ED physicians and neurologists knew the risk of thrombolysis better than general practitioners [86]. But the vast majorities of stroke patients in United States are treated in their acute stages by non-neurologists (such as primary care physicians, either internists or family physicians). Only 11% of acute stroke patients are treated by a neurologist [54]. Thus, the American Stroke Association recommends that training and education about acute ischemic stroke management should be provided to all physicians who might treat these patients. Acute stroke teams and specialized stroke units should be setup in order to provide prompt consultation and accurate stroke care; CT scans should be available on a 24-hour-per-day, 7-day-per-week basis. Hospitals lacking facilities for thrombolysis should transfer their patients to more equipped hospitals [29, 36, 43].

4.4 Outcomes of IV tPA therapy

When comparing the outcomes between patients treated with tPA and those not treated, tPA-treated patients had worse outcomes. They had higher in-hospital mortality rate (9.3% vs 1.4%) and longer hospital stay (7.2 vs 4.2 days). More tPA treated patients had higher modified Rankin Scale (MRS of 4-5: 51.3% vs 20.3%) and worse functional status at discharge (not able to ambulate 23.7% vs 8.2%), and they were less likely to be discharged back to home (56.4% vs 76.7%) and more likely to be discharged to nursing home (12.8% vs 6.8%). However no conclusions can be made based on this data,

because information related to pre-treatment stroke severity was missing in a majority of the eligible patients in our study (only 16% had a NIHSS score documented). In the NINDS trial, there was no significant improvement in patients treated with tPA in the first 24 hours after treatment, but tPA-treated patients had less disability observed at 3-months [20]. Thus it would be inappropriate to compare the modified Rankin scale (MRS) and functional status at discharge between these two groups of patients without the information about stroke severity and outcomes at 3-month.

4.5 Study Strengths and Limitations

The strength of this study is that the data are derived from one of the four prototypes for the Paul Coverdell National Acute Stroke Registry. A standardized data collection instrument was used, and the feasibility of prospective case ascertainment and data collection procedures was pilot tested. Prospectively collected data from a representative sample of hospitals across Michigan should reflect "real life" practice in acute stroke care and treatment.

This study also has limitations. First, our study was based on analysis of a small number of tPA patients and limited clinical factors. No information of patient knowledge of stroke signs and symptoms was available, and no information about treating physician attitudes toward tPA therapy was documented, thus we can't determine what directly cause the lack of documentation of stroke onset, delayed presentation, in-hospital delay and low overall tPA use. Second, poor documentation of NIHSS score in our study limited the comparison of patients' outcome between tPA treated and non-treated groups. Without adjusting for stroke severity using the NIHSS score, and/or size and the location of the ischemic lesion, it would be invalid for us to conclude that tPA was a cause of the

worse outcomes after treatment, except of course for the expected complications of tPA, i.e. ICH and systematic hemorrhage after treatment.

In conclusion, the use of IV tPA therapy among acute stroke patients is still very low. The primary reasons for patients being excluded from tPA treatment is that of patients did not arrive at ED within 3 hours after stroke onset and/or had no documented onset time. Other reasons include in-hospital delay and physicians' reluctance to tPA use among potentially eligible patients. Among all eligible patients, being male, use of EMS, and more rapid presentation were all significantly associated with tPA use. ICH rate after treatment was low in our study. Public education about the stroke warning sings and symptoms might decrease the pre-hospital delay, and further refinement of the infrastructure of stroke care delivery system, including physician education, could increase tPA use.

Table 4.1. Intracerebral Hemorrhage Rates after IV tPA.

Study, year	Study Type	Patients NO	Patients With ICH, %	Patients With Symptomatic ICH, %	Mortality rate
NINDS, 1995[20]	Randomized controlled trial	312	11	6	17
Houston, 1998[42]	Prospective Cohort	30	10	7	23
Cologne, 1998[41]	Single center experience	100	11	5	12
STARS, 1999[38]	Prospective cohort	296	10	3	13
Multicenter Survey, 1999[44]	Retrospective survey	189	9	6	NA
Cleveland, 2000[39]	Historical prospective cohort	70	22	16	15.7
Houston, 1996-2000[59]	Prospective Cohort	269	NA	5.6	15
OSF network, 2000[48]	Community hospital network	57	9	5	NA
Cleveland Update, 2003[40]	Retrospective chart review	47	NA	3	NA
MASCOTS, 2003	Prospective Registry	43	5	2	9.3

APPENDIX A

Hospital Survey for Paul Coverdell Stroke Registry Prototypes

Hospital Survey for Paul Coverdell Stroke Registry Prototypes

Hospital Name: _____ Date Completed: ___/___/_____

Name/Title of person completing this form:

_____

Others consulted:

_____

Address: _____

Phone:_____ Fax:_____ Email:

(*Please check the appropriate response*)

1. Does your hospital an acute stroke team?
   [ ] Yes
   [ ] No
   [ ] Unsure

   IF YES,

   1a. Is there a Neurologist on the Stroke Team?
   [ ] Yes
   [ ] No

   1b. Is there an Emergency Department physician on the Stroke Team?
   [ ] Yes
   [ ] No

2. Does your hospital have written guidelines in place for the emergency treatment of stroke?
   [ ] Yes
   [ ] No

3. Does your hospital have written guidelines (e.g., critical pathways, clinical pathways) for the subsequent, in-hospital management of stroke?
   [ ] Yes
   [ ] No

4. Please describe the availability of the following types of physicians to assist in the management of acute stroke (ischemic or hemorrhagic).

Neurologist:

[ ] 24 hours/7 days on premises

[ ] 24 hours/7 days on pager

[ ] Only available on page certain days/times

[ ] Not available

Neurosurgeon to assist in the management of acute stroke:

[ ] 24 hours/7 days on premises

[ ] 24 hours/7 days on pager

[ ] Only available on page certain days/times

[ ] Not available

Vascular Surgeon or Endovascular Specialist:

[ ] 24 hours/7 days on premises

[ ] 24 hours/7 days on pager

[ ] Only available on page certain days/times

[ ] Not available

Radiologist/Neuroradiologist to interpret images:

[ ] 24 hours/7 days on premises

[ ] 24 hours/7 days on pager or by tele-radiology

[ ] Only available on page certain days/times

[ ] Not available

Critical Care Physician:

[ ] 24 hours/7 days on premises

[ ] 24 hours/7 days on pager

[ ] Only available on page certain days/times

[ ] Not available

5. Does your hospital have a CT Scan on hospital grounds available and easily accessible to perform and provide CT results on stroke patients emergently?

[ ] Yes

[ ] No

IF YES,

4a. Is a CT Technician available?

[ ] 24 hours/7 days on premises

[ ] 24 hours/7 days on pager

[ ] Only available on page certain days/times

6. Does your hospital have a MR Imaging on hospital grounds available and easily accessible to perform and provide MR results on stroke patients emergently?

[ ] Yes

[ ] No

IF YES,

5a. Is a MR Technician available?

[ ] 24 hours/7 days on premises

[ ] 24 hours/7 days on pager

[ ] Only available on page certain days/times

7. Is intravenous t-PA in use at your hospital for the treatment of acute ischemic stroke?

[ ] Yes

[ ] No

IF YES,

6a. Is this therapy available 24 hours per day?

[ ] Yes

[ ] No

6b. In addition to intravenous t-PA, is catheter-based therapy for acute ischemic stroke available at your hospital?

[ ] Yes

[ ] No

8. Does your hospital have a written intravenous t-PA stroke protocol in place?

[ ] Yes

[ ] No

9. Was your hospital involved in stroke quality improvement programs prior to participating in the *Coverdell* program?

[ ] Yes

[ ] No

10. In hospital rehabilitation therapies available to your stroke patients: (*check all that apply*)

[ ] Speech therapy

[ ] Physical therapy

[ ] Occupational therapy

[ ] Social worker, discharge planner

[ ] Case manager nurse practitioner or clinical nurse specialist

11. Does your hospital have a database or registry for tracking any of the following:

(*check all that apply*)

[ ] Number of patients admitted with stroke

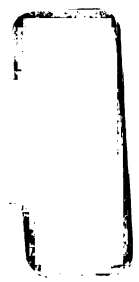
[ ] Type of stroke each patient experienced

[ ] Type of treatments provided

[ ] Time lines for providing treatments

[ ] Measurement of outcomes

Additional Comments:



APPENDIX B

MASCOTS DATA ELEMENTS

MASCOTS DATA ELEMENTS

Study ID |__|__| - |__|__|__|__|

A. DEMOGRAPHIC DATA

IN HOSPITAL ONLY QUESTIONS (A1-A3)

A1. Name (First_____, Middle initial_____, Last_____)

A2. Medical Record # (numeric)_____

A3. DOB ___ / ___ / _____

A4. Age (years): ..... |__|__|__|

A5. Gender:

- Male ..... []
- Female ..... []
- ND ..... []

A6. Hispanic or Latino origin:

- No ..... []
- Yes ..... []
- ND ..... []

A7. Race: (CHECK ALL THAT APPLY)

- White ..... []
- Black or African American ..... []
- Asian ..... []
- American Indian or Alaskan Native ..... []
- Native Hawaiian or Pacific Islander ..... []
- Other (Specify: _____ ..... []
- ND ..... []

A8. ZIP Code of Residence: ..... |__|__|__|__|__|

A9. Health Insurance Status: (CHECK ALL THAT APPLY)

- Medicare ..... []
- Medicaid ..... []
- Blue Cross/Blue Shield ..... []
- HMO/PPO (Specify: _____ ..... []
- Other private/commercial (Specify: _____ ..... []
- Other (Specify: _____ ..... []
- Self Pay ..... []
- ND ..... []

A10. Place of residence:

- Nursing home ..... []
- Other ..... []
- ND ..... []

A11. Where did stroke occur?

- Home ..... []
- Work ..... []
- In-hospital ..... []
- Other (Specify: _____ ..... []

ND..... []

IF IN-HOSPITAL STROKE, THEN GO TO SECTION D →

A12. Arrival Mode: (CHECK ONLY ONE)
Ambulance (EMS)..... []
Air (EMS)..... []
Other..... []
ND..... []

A13. Was this a Direct Admit:
No..... []
Yes..... []

IF DIRECT ADMIT, THEN GO TO SECTION E →

IF A12 = OTHER OR ND, THEN GO TO SECTION C →

A14. Was this a hospital transfer?
No..... []
Yes..... []
IF YES:
A14a. What was the transferring diagnosis?_____

IF HOSPITAL TRANSFER AND ORIGINAL TRIP SHEET IS NOT AVAILABLE, THEN GO TO SECTION C →

B. EMS RUN SHEET

B1. What type of run was this?
Basic Life Support (BLS)..... []
Advanced Life Support (ALS)..... []
ND..... []

B2. What was the dispatch priority level?
Level 1 (Red)..... []
Level 2 (Yellow)..... []
Level 3 (Green)..... []
ND..... []

B3. Is EMS run sheet available?
No..... []
Yes..... []

IF NO, THEN GO TO SECTION C →

B4. Date and time call received by EMS:..... ___ / ___ / _____ ___ : ___ ND[]

B5. Date and time of EMS Dispatch:..... ___ / ___ / _____ ___ : ___ ND[]

B6. ZIP Code of Dispatch:..... |__|__|__|__|__| ND[]

B7. Date and time of EMS first patient contact (defined as directly noted on first vital signs):..... ___ / ___ / _____ ___ : ___ ND[]

B8. Date and time of EMS Scene Departure: ___ / ___ / _____ ___ : ___ ND[]

B9. Date and time EMS ED Arrival: ___ / ___ / _____ ___ : ___ ND[]

B10. Initial Blood Pressure:
Systolic BP (mmHg) |__|__|__| ND[]
Diastolic BP (mmHg) |__|__|__| ND[]

B11. Heart Rate (beats per minute): |__|__|__| ND[]

B12. Was time of stroke onset documented?
No []
Yes []
IF YES:
B12a. Record specific time: ___ : ___ or record exact text _____

B13. Was a stroke scale recorded?
No []
Yes []
IF YES:
B13a. Which one? (CHECK ALL THAT APPLY)
Cincinnati (CPSS) []
L.A. (LAPSS []
Glasgow Coma Scale (GCS) []
Other (Specify:_____ []

B14. Neuro specific exam items evaluated and documented?
Facial Droop evaluated []Yes []No
Focal extremity weakness evaluated []Yes []No
Speech abnormality evaluated []Yes []No

B15. Was blood sugar check checked?
No []
Yes []

B16. Was the 'Nature of Call' Stroke, R/O stroke, or TIA?
No []
Yes []
ND []

B17. Were any of the following acute S/S reported in the patient's history?
Headache []Yes []No []ND
Unilateral weakness []Yes []No []ND
Unilateral numbness []Yes []No []ND
Speech abnormality []Yes []No []ND
Visual disturbance []Yes []No []ND
Monocular blindness []Yes []No []ND
Dizziness/Vertigo []Yes []No []ND
Acute onset inability to walk []Yes []No []ND

B18. Were any of the following physical findings present on examination as documented by EMS personnel?
Unilateral weakness []Yes []No []ND
Unilateral numbness []Yes []No []ND
Speech abnormality []Yes []No []ND

Visual disturbance ..... []Yes []No []ND
Monocular blindness ..... []Yes []No []ND
Dizziness/Vertigo ..... []Yes []No []ND
Acute onset inability to walk ..... []Yes []No []ND
Ataxia ..... []Yes []No []ND
Confusion ..... []Yes []No []ND
Altered level of consciousness ..... []Yes []No []ND

C. EMERGENCY DEPARTMENT TRIAGE

C1. Date and time of arrival in ED: ..... ___ / ___ / _____ ___ : ___ ND[]

C2. Chief Complaint: _____

C3. Date and time first seen by ED Physician: ..... ___ / ___ / _____ ___ : ___ ND[]
IF ND:
C3a. Date and time of first order: ..... ___ / ___ / _____ ___ : ___ ND[]

C4. Evidence in record of consultation or discussion with acute stroke team?
No ..... []
Yes ..... []

IF YES:
C4a. Date and time of acute stroke consultation: .. ___ / ___ / _____ ___ : ___ ND[]

C4b. Who was first consulted: (CHECK ONLY ONE)
Neurologist ..... []
ED Physician ..... []
Neurosurgery ..... []
Other (Specify: _____ ..... []
ND ..... []

C4c. Mode of communication:
In person ..... []
By phone ..... []
Telemedicine ..... []
ND ..... []

C5. Was stroke or stroke-like symptoms documented in the ED evaluation?
No ..... []
Yes ..... []

C6. Was stroke/TIA one of the documented ED diagnoses?
No ..... []
Yes ..... []

C7. Primary ED Admitting Diagnosis (ICD-9 Code or text): ..... _____ ND[]

D. IN-HOSPITAL STROKE

D1. Date of hospital admission: ..... ___ / ___ / _____ ND[]

D2. Admitting Diagnosis (text and/or ICD-9 Code): ..... _____

D3. Date and time first stroke S/S documented in hospital: ___ / ___ / _____ ___ : ___ ND[]

D4. What major procedures/interventions had patient undergone prior to the onset of stroke? (CHECK ALL THAT APPLY)

Surgery (Specify: _____ Date___ / ___ / _____
Diagnostic (Specify: _____ Date___ / ___ / _____
Therapeutic (Specify: _____ Date___ / ___ / _____
Other (Specify: _____ Date___ / ___ / _____

D5. Other comments: _____

E. INITIAL BRAIN IMAGING

E1. Type of initial brain image:

CT ..... []
MRI ..... []
Not performed ..... []
Other (Specify: _____ ..... []
ND ..... []

E2. Date and time of initial brain imaging: ..... ___ / ___ / _____ ___ : ___ ND[]
Image obtained from outside/transferring hospital ..... []

IF DATE/TIME IMAGE PERFORMED IS NOT AVAILABLE, THEN:

E2a. Date and time patient left ED to radiology for initial image:
___ / ___ / _____ ___ : ___ ND[]

E2b. Date and time patient left radiology following initial image:
___ / ___ / _____ ___ : ___ ND[]

E3. Date and time of earliest documentation of imaging results known to treating physician:
___ / ___ / _____ ___ : ___ ND[]

E4. Evidence of intracranial hemorrhage or acute blood on initial image?

No ..... []
Yes ..... []
ND ..... []

E5. Image results: (CHECK ALL THAT APPLY)

Normal ..... []
Acute / subacute infarct ..... []
Chronic old infarct ..... []
SAH ..... []
ICH ..... []
Other (Specify:_____ .... []
ND ..... []

F. PRESENTING SIGNS AND SYMPTOMS

F1. Is a specific date and time of onset of acute stroke S/S documented or is an estimated time accurate to within a six hour window available?

Yes – specific time ..... []
Yes – estimated time ..... []
No ..... []

IF YES – SPECIFIC TIME:

F1a. Specific date and time of onset: ..... ___ / ___ / _____ ___ : ___

F1b. What was the source of this information?

Witnessed ..... []
Patient self-report ..... []
ND ..... []

IF YES – ESTIMATED TIME:

F1c. Estimated date of onset: ..... ___ / ___ / _____

F1d. Estimated time of day of onset (i.e., six hour window):

Morning (6am-11:59am) ..... []
Afternoon (noon-5:59pm) ..... []
Evening (6pm-11:59pm) ..... []
Overnight (midnight-5:59am) ..... []

IF NO:

F1e. Estimated date of onset or date last seen normal: ..... ___ / ___ / _____
or Date last seen normal: ..... ___ / ___ / _____ Unknown [] or ND[]

F2. Source of documentation from chart abstraction: (CHECK ONLY ONE)

Treating Neurologist or Stroke Team ..... []
Treating Physician (ED Physician) ..... []
Treating RN ..... []
EMS run sheet ..... []
Other (Specify: _____ ..... []
ND ..... []

F3. Date first NIH Stroke Scale (NIHSS) administered: ..... ___ / ___ / _____ ND[]

F4. First NIHSS Total Score recorded by health care provider: ..... |__|__| ND[]

G. THROMBOLYTIC TREATMENT

IF E5 = ICH OR SAH, THEN GO TO SECTION H →

G1. Did patient receive thrombolytic therapy?

No ..... []
Yes ..... []

IF NO, THEN GO TO G1c:

IF YES:

G1a. Date and time of initiation: ..... ___ / ___ / _____ ___ : ___ ND[]

G1b. Route of thrombolytic delivery: (CHECK ONLY ONE)

Intravenous ..... []
Intra-arterial (via angiography) ..... []
Intravenous and Intra-arterial ..... []
ND ..... []

G1c. Did patient have complications from thrombolytic treatment:

No ..... []
Yes ..... []

IF YES:

G1d. What were the complications? (CHECK ALL THAT APPLY)

Symptomatic intracranial hemorrhage ..... []
Life threatening systematic hemorrhage ..... []

Any other hemorrhage mentioned in the record post-treatment .....[]

Comment:_____

IF NO TO G1:

G1e. Physician documented reasons indicated for non-Treatment with Thrombolytics (these are not necessarily contraindications): (CHECK ALL THAT APPLY)

1) Time .....[]
2) Uncontrolled hypertension .....[]
3) Rapid improvement .....[]
4a) CT findings – Hemorrhage .....[]
4b) CT findings – Other .....[]
5) Stroke severity – Too mild .....[]
6) Stroke severity – Too severe .....[]
7) Seizure at onset .....[]
8) Recent surgery/Trauma (< 15 days) .....[]
9) Recent IC Surgery (3 mo.) head trauma/stroke .....[]
10) Pt./Family refused .....[]
11) Consent non obtainable .....[]
12) History of intracranial hemorrhage or brain aneurysm or vascular malformation or brain tumor .....[]
13) Age .....[]
14) Active internal bleeding (<22 days) .....[]
15) Platelet count (<100,000) .....[]
16) Abnormal aPTT or PT .....[]
17) Glucose < 50mg/dl or > 400 mg/dl .....[]
18) No IV access .....[]
19) Life expectancy < 1 year or severe comorbidity .....[]
20) Other (Specify_____ ...[]
ND .....[]

IF MORE THAN ONE CHECKED:

G1f. What was the primary reason? ..... |__|__| ND[]

G1g. Comments for non-treatment reasons: _____

G2. Investigational therapy for acute ischemic stroke (clinical trial):

No .....[]
Yes .....[]

H. IN-HOSPITAL DIAGNOSIS, PROCEDURES AND TREATMENTS

H1. Was patient on a cardiac monitor?

No .....[]
Yes .....[]
ND.....[]

H2. Was AFib present during hospitalization?

No .....[]
Yes .....[]
ND.....[]

IF YES:

H2a. Was a warfarin (Coumadin), heparin or heparinoids treatment given:

No .....[]

Yes ..... []
ND ..... []

IF NO:

H2b. Reason indicated for non-treatment (CHECK ALL THAT APPLY)

Risk for bleeding ..... []
Risk for falls ..... []
Mental status ..... []
Liver disease ..... []
Terminal illness ..... []
Patient refused, reason not specified ..... []
Patient refused, did not want risk ..... []
Discontinued due to bleeding ..... []
On ASA as a regular medication ..... []
Arthritis requiring NSAIDs or ASA ..... []
Other (Specify:_____ ..... []
ND ..... []

H2c. Comment reasons for non-treatment: _____

H3. Was cerebrovasculature investigated?

No ..... []
Yes ..... []
ND ..... []

IF YES:

H3a. Which of the following tests were documented to evaluate the cerebrovasculature? (CHECK ALL THAT APPLY)

Duplex ultrasound ..... []
MR Angiogram ..... []
CT Angiogram ..... []
Cerebral Angiogram ..... []
Transcranial Doppler ..... []
ND ..... []

H3b. Was an intervention considered (=discussed, performed or planned)?

No ..... []
Yes ..... []
ND ..... []

IF YES:

H3c. What procedure?

Endarterectomy ..... []
Stenting ..... []
Angioplasty ..... []
Medical ..... []
Surgical Intervention ..... []
ND ..... []

H4. Was screening for dysphagia (Swallow test) performed (bedside testing sufficient)?

No ..... []
Yes ..... []
ND ..... []

H5. Were anti-thrombotic treatment(s) given during hospitalization?

No ..... []
Yes ..... []
ND ..... []

IF YES:

H5a. Time of initiation of anti-thrombotic treatment? (CHECK ONLY ONE)

0-24hrs ..... []
>24hrs ..... []
ND ..... []

H5b. Type of anti-thrombotic treatments given: (CHECK ALL THAT APPLY)

Aspirin ..... []
Aggrenox ..... []
Warfarin (Coumadin) ..... []
Ticlopidine (Ticlid) ..... []
Dipyridamole/Persantine ..... []
Clopidogrel (Plavix) ..... []
Heparin SQ ..... []
Heparin IV ..... []
LMW Heparin ..... []
Other anti-thrombotic (Specify:_____ ..... []
Unknown type ..... []

H6. Was DVT prophylaxis initiated by 2nd hospital day?

No ..... []
Yes ..... []
N/A – (patient ambulating or already receiving anticoagulant) ..... []
ND ..... []

H7. Was a neurologist or neurosurgeon involved in the care of the patient during hospitalization?

No ..... []
Yes ..... []
ND ..... []

H8. Was echocardiography performed during hospitalization?

No ..... []
Yes ..... []
ND ..... []

I. IN-HOSPITAL COMPLICATIONS

I1. Was DVT/PE documented during hospitalization?

No ..... []
Yes ..... []

IF YES:

I1a. Confirmed by: (CHECK ALL THAT APPLY)

U/S ..... []
Venous imaging ..... []
Other (Specify:_____ ..... []

I2. Clinical mention of pneumonia and treatment with antibiotic for that problem?

No ..... []
Yes ..... []

I3. Clinical mention of UTI and treatment with antibiotic for that problem?

No ..... []
Yes ..... []

J. MEDICAL HISTORY

J1. Medications at admission: (WRITE UP TO 24)

1) _____	13) _____
2) _____	14) _____
3) _____	15) _____
4) _____	16) _____
5) _____	17) _____
6) _____	18) _____
7) _____	19) _____
8) _____	20) _____
9) _____	21) _____
10) _____	22) _____
11) _____	23) _____
12) _____	24) _____

J2. Documented past medical history (determined by physician/RN admission or discharge notes):

(1) Stroke/TIA/VBI ..... Yes [] No [] ND []
(2) Myocardial Infarction (MI) ..... Yes [] No [] ND []
(3) Coronary Artery (Heart) Dis (CAD or CHD) ..... Yes [] No [] ND []
(4) Atrial Fibrillation (AF) ..... Yes [] No [] ND []
(5) Congestive Heart Failure (CHF) ..... Yes [] No [] ND []
(6) Valve Prosthesis ..... Yes [] No [] ND []
(7) Hypertension (HTN) ..... Yes [] No [] ND []
(8) Dyslipidemia ..... Yes [] No [] ND []
(9) Diabetes Mellitus ..... Yes [] No [] ND []
(10) DVT/PE ..... Yes [] No [] ND []
(11) Other Cardiac Procedures ..... Yes [] No [] ND []

J3. Smoking status prior to presentation?

Never ..... []
Former (Quit when? |__|__| years ago) ..... []
Current (Pack Years |__|__|__| or Years duration |__|__| and/or cigs per day |__|__|)..... []
Nonsmoker ..... []
ND ..... []

K. SECONDARY STROKE PREVENTION TREATMENTS PLANNED OR INITIATED AT DISCHARGE

IF HISTORY OF AFIB (J2) OR AFIB PRESENT IN HOSPITAL (H2) THEN K1, ELSE GOTO K2:

K1. Was patient discharged on a warfarin (Coumadin), heparin or heparinoids treatment?

No ..... []
Yes ..... []
ND ..... []

IF NO:

K1a. Reason indicated for non-treatment of AFib (CHECK ALL THAT APPLY)

- Risk for bleeding [ ]
- Risk for falls [ ]
- Mental status [ ]
- Liver disease [ ]
- Terminal illness [ ]
- Patient refused, reason not specified [ ]
- Patient refused, did not want risk [ ]
- Discontinued due to bleeding [ ]
- On ASA as a regular medication [ ]
- Arthritis requiring NSAIDs or ASA [ ]
- Other (Specify:_____) [ ]
- ND [ ]

K1b. Comments on non-treatment: _____

K2. Was patient on antithrombotic medications at discharge?

- No [ ]
- Yes [ ]
- ND [ ]

IF YES:

K2a. What antithrombotic treatments were listed? (CHECK ALL THAT APPLY)

- Aspirin [ ]
- Aggrenox [ ]
- Warfarin (Coumadin) [ ]
- Ticlopidine (Ticlid) [ ]
- Dipyridamole/Persantine [ ]
- Clopidogrel (Plavix) [ ]
- Heparin SQ [ ]
- Heparin IV [ ]
- LMW Heparin [ ]
- Other anti-thrombotic (Specify:_____) [ ]
- Unknown type [ ]

IF NO:

K2b. Why not? (CHECK ALL THAT APPLY)

- Transferred to another facility [ ]
- Peptic ulcer (current) [ ]
- Intracranial surgery/biopsy (current) [ ]
- Refused treatment [ ]
- Terminal/comfort care on the day of arrival or during the stay [ ]
- Unrepaired intracranial aneurysm (history or current) [ ]
- Terminal illness (life expectancy less than 6 months) [ ]
- Aortic dissection (current) [ ]
- Discharge against medical advice [ ]
- CVA, hemorrhagic (history or current) [ ]
- Planned surgery within 7 days following discharge [ ]
- Allergy to or complication r/t aspirin, ticlopidine, clopidogrel, dipyridamole and warfarin (history or current) [ ]
- Brain/CNS cancer (history or current) [ ]
- Antithrombotics (Aggrenox, aspirin, dipyridamole, clopidogrel, ticlopidine) considered by not prescribed [ ]
- Bleeding disorder [ ]
- Extensive/metastatic cancer (history or current) [ ]
- Risk for bleeding (current) [ ]
- Hemorrhage, any type (history or current) [ ]
- Other (Specify:_____) [ ]
- ND (Unknown) [ ]

K2c. Comments on non-treatment: _____

IF J3 CURRENT SMOKER OR QUIT < 1 YEAR THEN K3, ELSE GOTO K4:

K3. Was smoking cessation, counseling or treatment planned in discharge notes?

No .....[]
Yes .....[]
ND.....[]

IF YES:

K3a. What? (CHECK ALL THAT APPLY)

Transdermal Nicotine Patch (Habitrol, Nicoderm, Nicotrol, Prostep)...[]
Nicotine Polacrilix (Nicorette Gum).....[]
Nicotine Nasal Spray .....[]
Nicotine Inhaler .....[]
Bupropion (Zyban) .....[]
Referral- counseling .....[]
Referral- other .....[]
Other (Specify:_____.[]

K4. Was any lipid investigation conducted during hospitalization?

No .....[]
Yes .....[]
ND.....[]

IF YES:

K4a. Total Cholesterol (mg/dl):.....|__|__|__| ND[]

K4b. HDL (mg/dl): .....|__|__|__| ND[]

K4c. LDL (mg/dl):.....|__|__|__| ND[]

K4d. Triglycerides (mg/dl): .....|__|__|__| ND[]

K5. Was patient on lipid altering medications at discharge?

No .....[]
Yes .....[]
ND.....[]

IF YES:

K5a. What lipid altering agents? (WRITE UP TO THREE)

1) _____ 2) _____ 3) _____

K6. Was patient on anti-hypertensive medications at discharge (planned treatment listed in Physician or RN notes)?

No .....[]
Yes .....[]
ND.....[]

IF YES:

K6a. Type of anti-HTN treatments? (RECORD UP TO THREE MEDS PER CLASS)

ACE Inhibitor..... 1)_____ 2)_____ 3)_____
Beta Blockers..... 1)_____ 2)_____ 3)_____
Ca++ Chan Block. 1)_____ 2)_____ 3)_____
Diuretics ..... 1)_____ 2)_____ 3)_____
Other ..... 1)_____ 2)_____ 3)_____

IF NO:

K6b. Why not? _____

IF HISTORY OF DIABETES (J2) OR DIAGNOSED IN-HOSPITAL, THEN K7, ELSE GO TO SECTION L:

K7. Was patient on diabetes medication at discharge?

No .....[]
Yes .....[]
ND.....[]

IF YES:

K5a. What diabetes medications? (WRITE UP TO THREE)

1) _____ 2) _____ 3) _____

K8. What was the A1C level (%) during hospitalization? ..... |__|__|.|__| ND[]

L. DISCHARGE INFORMATION

L1. Date of Hospital Discharge: ..... ___ / ___ / _____ ND[]

L2. Hospital attending service at time of discharge: (CHECK ONLY ONE)

Neurology .....[]
Neurosurgery .....[]
Neuro ICU .....[]
CCU .....[]
Internal Med.....[]
General Med .....[]
Family Practice .....[]
Hospitalist .....[]
Stroke Service Unit .....[]
Geriatric .....[]
Other (Specify: _____ .....[]

L3. Was a Stroke Pathway Used?

No .....[]
Yes .....[]

L4. Discharge Status (destination): (WRITE IN CODE NUMBER) ..... |__|__|ND[]

IF DISCHARGE STATUS IS #5=(DISCHARGE/TRANSFER TO ANOTHER TYPE OF INSTITUTION FOR INPATIENT CARE OR REFERRED FOR OUTPATIENT SERVICES TO ANOTHER INSTITUTION):

L4a. Was patient discharge to a hospital based acute rehabilitation service?

No .....[]
Yes.....[]
ND ..... []

L5. Modified Rankin at discharge: (CHECK ONLY ONE)

(0) No symptoms at all..... []
(1) No significant disability despite symptoms: able to carry out all usual duties and activities..... []
(2) Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance..... []
(3) Moderate disability: requiring some help, but able to walk without assistance..... []
(4) Moderate to severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance..... []
(5) Severe disability: bedridden, incontinent, and requiring constant

nursing care and attention ..... []
(6) Death ..... []
Unable to ascertain ..... []

L6. Functional status at discharge: (CHECK ONLY ONE)
Able to ambulate independently ..... []
Ambulates with assistance from another individual ..... []
Not able to ambulate ..... []
N/A (expired) ..... []
Unknown/Don't know ..... []

L7. Functional status pre-stroke: (CHECK ONLY ONE)
Was able to ambulate independently ..... []
Ambulated with assistance from another individual ..... []
Was not able to ambulate ..... []
Unknown/Don't know ..... []

L8. Principal Hospital Discharge Diagnoses Code (ICD-9): _____
IF NOT STROKE:
L8a. Was a stroke code listed as a secondary diagnosis?
No ..... []
Yes ..... []
IF YES:
L8b. What was the ICD-9 code? _____

L9. Coverdell stroke sub-type diagnosis: (CHECK ONLY ONE)
(1) Ischemic Stroke ..... []
(2) ICH ..... []
(3) SAH ..... []
(4) Stroke of uncertain type ..... []
(5) TIA ..... []
(6) Hemorrhagic Stroke of uncertain type ..... []
(7) Ischemic Stroke of uncertain type ..... []
(8) Not a stroke ..... []

L9a. Comment pertaining to diagnosis: _____

L10. Documented evidence in the chart of poor patient prognosis influencing diagnosis, treatment and/or follow-up: (CHECK ALL THAT APPLY)
None found ..... []
Terminal/comfort care on the day of arrival or during the stay ..... []
Terminal illness (life expectancy less than 6 months) ..... []
DNR orders ..... []
Extensive/metastatic cancer (history or current) ..... []
Severity of stroke ..... []
Other (Specify: _____ ..... []

M. **SUMMARY COMMENTS**

_____

_____

_____

********** END **********

REFERENCES

1. Decline in deaths from heart disease and stroke-United States, 1990-1999. MMWR 1999; 48:649-56.

2. American Stroke Association. Heart Disease and Stroke statistics, 2003:15-17

3. Michigan Department of Community Health (MDCH). MDCH Epidemiology of Stroke Fact Sheet, 2002.

4. Centers for Disease Control and Prevention (CDC). Atlas of Stroke Mortality: Racial, Ethnic, and Geographic Disparities in the United States, 2003.

5. CDC/NCHS. Healthy people Statistical notes. 2002.

6. Muntner P, Garrett E, Klag MJ, Coresh J. Trends in Stroke Prevalence Between 1973 and 1991 in the US Population 25 to 74 Years of Age. Stroke 2002;33:1209-1213.

7. CDC/NCHS. Prevalence of Disabilities and Associated Health Conditions Among Adults --- United States, 1999. MMWR, Vol, No7, , 2001, . 2001;50:117.

8. Centers for Medicare & Medicaid Services (CMS). Health Care Financing Review. Statistical Supplement 2000

9. Del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: A Phase II Randomized Trial of Recombinant Pro-Urokinase by Direct Arterial Delivery in Acute Middle Cerebral Artery Stroke. Stroke 1998; 29:4-11.

10. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial Prourokinase for Acute Ischemic Stroke: The PROACT II Study: A Randomized Controlled Trial. JAMA 1999; 282:2003-2011.

11. Cloft HJ, Tomsick TA, Kallmes DF, Goldstein JH, Connors JJ. Assessment of the Interventional Neuroradiology Workforce in the United States: A Review of the Existing Data. AJNR Am J Neuroradiol 2002;23:1700-1705.

12. Multicenter Acute Stroke Trial-Italy Group (MAST-I). Randomized controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischemic stroke. Lancet 1995; 346:1509-1514.

13. The Multicenter Acute Stroke Trial - Europe Study Group (MAST-E). Thrombolytic Therapy with Streptokinase in Acute Ischemic Stroke. N Engl J Med 1996; 335:145-150.

14. Donnan GA, Davis SM, Chambers BR, et al. Streptokinase for acute ischemic stroke with relationship to time of administration: Australian Streptokinase (ASK) Trial Study Group. JAMA 1996; 276:961-966.

15. Loscalzo J. BE. Tissue plasminogen activator. N Engl J Med 1988; 319:925-931.

16. Mori E YM, Tabuchi M. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. Neurology 1992;42:976-982.

17. Yamaguchi T HT, Kiuchi H. Japanese Thrombolysis Study Group. Intravenous Tissue Plasminogen Activator Ameliorates the Outcome of Hyperacute Embolic Stroke. Cerebrovasc Dis 1993; 3:269-272.

18. Enropean Cooperative Acute Stroke Study (ECASS). Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. JAMA 1995; 274:1017-1025.

19. Haley EC, Jr., Brott TG, Sheppard GL, et al. Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. The TPA Bridging Study Group. Stroke 1993; 24:1000-4.

20. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group. Tissue Plasminogen Activator for Acute Ischemic Stroke. N Engl J Med 1995; 333:1581-1588.

21. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: The NINDS rt-PA Stroke Study. Neurology 2000; 55:1649-1655.

22. 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.

23. Clark WM, Albers GW for the ATLANTIS Stroke Study Investigators. The ATLANTIS rt-PA (Alteplase) Acute Stroke Trial - Final Results. Stroke 1999; 30:234.

24. Clark WM, Wissman S, Albers GW, et al. 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; 282:2019-2026.

25. Haley E, Jr, Brott T, Sheppard G, et al. Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. The TPA Bridging Study Group. Stroke 1993; 24:1000-1004.

26. Hacke Werner BT, Caplan Louis et al. Thrombolysis in acute ischemic stroke: controlled trials and clinical experience. Neurology 1999; 539:S3-S14.

27. Wardlaw JM, del Zoppo GJ, Yamaguchi T, et al. Yamaguchi T, Berge E. Thrombolysis in acute ischemic stroke. Cochrane Database Systematic Rev 2000; 2.

28. NINDS. Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke. December 12-13, 1996.

29. Adams HP BT, Furlan AJ, et al. Guidelines for thrombolytic therapy for acute stroke: A supplement for the guidelines for the management of patients with acute ischemic stroke. A statement of healthcare professionals from a special writing group of the Stroke Council of the American Heart Association. Stroke 1996; 27:1711-1718.

30. Subcommittee of the American Academy of Neurology. Report of the Quality Standards Subcommittee of the American Academy of Neurology: Practice advisory: Thrombolytic Therapy for Acute ischemic stroke -summary statement. Neurology 1996; 46:835-839.

31. American College of Emergency physicians (ACEP) Board of Directors. ACEP Policy Statements. Use of Intravenous tPA for the management of Acute stroke in the Emergency Department. Approved by the ACEP Board of Directors, 2002.

32. American College of Emergency physicians (ACEP). Policy Resource and Education Papers. Use of Intravenous tPA for the management of Acute stroke in the Emergency Department. An explication of the Policy Statement. 2002.

33. Oscar Bnavente RH. Stroke: Part II. Management of acute ischemic Stroke. American Academy of Family Physicians. 1999.

34. The Canadian Stroke Consortium. Canadian Guidelines for Intravenous Thrombolytic Treatment in Acute Stroke: A Consensus Statement of The Canadian Stroke Consortium. Can. J. Neurol. Sci. 1998; 25:257.

35. Royal College of Physicians of London. National Clinical Guidelines for Stroke., 2000.

36. Harold P. Adams J, Robert J. Adams, and Thomas Brott, et al. Guidelines for the Early Management of Patients with Ischemic Stroke: A Scientific Statement From the Stroke Council of the American Stroke Association. Stroke 2003; 34:1056-1083.

37. Lopez-Yunez AM, Bruno A, Williams LS, Yilmaz E, Zurru C, Biller J. Protocol violations in community-based rtPA stroke treatment are associated with symptomatic intracerebral hemorrhage. Stroke 2001; 32:12-6.

38. Gregory Alers VB, Wayne Clark, et al. Intravenous Tissue-type plasminoen Activator for Treatment of Acute Stroke-STARS study. JAMA 2000; 283:1145-1150.

39. Irene Katzan AF, Lloyd LE, et al. Use of tPA for acute Ischemic stroke-The Cleveland Area Experience. JAMA 2000; 283:1151-1158.

40. Katzan IL, Hammer MD, Furlan AJ, Hixson ED, Nadzam DM. Quality Improvement and Tissue-Type Plasminogen Activator for Acute Ischemic Stroke: A Cleveland Update. Stroke 2003; 34:799-800.

41. Grond M, Stenzel C, Schmulling S, et al. Early Intravenous Thrombolysis for Acute Ischemic Stroke in a Community-Based Approach. Stroke 1998; 29:1544-1549.

42. Chiu D, Krieger D, Villar-Cordova C, et al. Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke: Feasibility, Safety, and Efficacy in the First Year of Clinical Practice. Stroke 1998; 29:18-22.

43. Alberts MJ. tPA in acute ischemic stroke: United States experience and issues for the future. Neurology 1998; 51:S53-5.

44. Tanne D, Bates VE, Verro P, et al. Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: A multicenter survey. Neurology 1999; 53:424-427.

45. Robert E O'Conner PM, Lanny Edelsohn. Thrombolytic therapy for acute ischemic stroke: Why the majority of patients remain ineligible for treatment. Annals of Emergency Medicine 1999; 33:9-14.

46. Newcommon N. TPA in acute ischemic stroke. A Calgary experience. Axone 2000; 21:73-5.

47. Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. Neurology 2001; 56:1015-20.

48. Wang DZ, Rose JA, Honings DS, Garwacki DJ, Milbrandt JC. Treating acute stroke patients with intravenous tPA. The OSF stroke network experience. Stroke 2000; 31:77-81.

49. Peter Heuschmann KB, Bjoern Misselwiz, et al. Frequency of Thrombolytic Therapy in Patients with Acute Ischemic Stroke and the Risk of In-Hospital Mortality. Stroke 2003; 34:1106-1112.

50. Koennecke H-C, Nohr R, Leistner S, Marx P. Intravenous tPA for Ischemic Stroke Team Performance Over Time, Safety, and Efficacy in a Single-Center, 2-Year Experience. Stroke 2001; 32:1074-1078.

51. The NINDS t-PA sStroke Study Group. Intracerebral Hemorrhage After Intravenous t-PA Therapy for Ischemic Stroke. Stroke 1997; 28:2109-2118.

52. Reed SD, Cramer SC, Blough DK, Meyer K, Jarvik JG, Wang DZ. Treatment With Tissue Plasminogen Activator and Inpatient Mortality Rates for Patients With Ischemic Stroke Treated in Community Hospitals Editorial Comment. Stroke 2001; 32:1832-1840.

53. Elly Engelstein JM, Joseph Jeret. Lack of tPA use for acute ischemic stroke in a community hospital: high incidence of exclusion criteria. American Journal of Emergency Medicine 2000; 18:257-260.

54. Mitchell JB, Ballard DJ, Whisnant JP, Ammering CJ, Samsa GP, Matchar DB. What Role Do Neurologists Play in Determining the Costs and Outcomes of Stroke Patients? Stroke 1996; 27:1937-1943.

55. Villar-Cordova C. Neurologists' Attitudes regarding tPA for acute ischemic stroke. Neurology 1998; 50:1491-1494.

56. Chaturvedi S bB, Femino L. Emergency physician attitudes toward thrombolytic therapy in acute stroke. J Stroke Cerebrovasc Dis. 1998; 7.

57. Wester P, Radberg J, Lundgren B, Peltonen M. Factors Associated With Delayed Admission to Hospital and In-Hospital Delays in Acute Stroke and TIA: A Prospective, Multicenter Study. Stroke 1999; 30:40-48.

58. Broderick J, Brott T, Kothari R, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: Preliminary First-Ever and Total Incidence Rates of Stroke among Blacks. Stroke 1998; 29:415-421.

59. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous Tissue-Type Plasminogen Activator Therapy for Ischemic Stroke: Houston Experience 1996 to 2000. Arch Neurol 2001; 58:2009-2013.

60. Koennecke HC, Nohr R, Leistner S, Marx P. Intravenous tPA for ischemic stroke team performance over time, safety, and efficacy in a single-center, 2-year experience. Stroke 2001; 32:1074-8.

61. Pancioli AM, Broderick J, Kothari R, et al. Public Perception of Stroke Warning Signs and Knowledge of Potential Risk Factors. JAMA 1998; 279:1288-1292.

62. Reeves M, Hogan Joanne G, Rafferty Ann P. Knowledge of stroke risk factors and warning signs among Michigan adults. Neurology 2002; 59:1547-1552.

63. Kothari R, Sauerbeck L, Jauch E, et al. Patients' Awareness of Stroke Signs, Symptoms, and Risk Factors. Stroke 1997; 28:1871-1875.

64. Wellwood I DM, Warlow CP. Perceptions and knowledge of stroke among surviving patients with stroke and their caregivers. . Age Ageing 1994; 23:293-298.

65. Williams LS, Bruno A, Rouch D, Marriott DJ, MAS DJ. Stroke Patients' Knowledge of Stroke: Influence on Time to Presentation. Stroke 1997; 28:912-915.

66. Jorgensen H, Nakayama H, Reith J, Raaschou H, Olsen T. Factors delaying hospital admission in acute stroke: the Copenhagen Stroke Study. Neurology 1996; 47:383-387.

67. Zweifler RM TB, Lyden PD, Rothrock JF. Relationship between time to medical evaluation and ischemic stroke severity: the UCSD Stroke Data Bank. J Stroke Cerebrovasc Dis. 1995; 5:111.

68. Saver JL BA, Feldmann E, Libman RB, Clarke WC, Grimsman K, Adams HP Jr. Time from stroke onset to arrival in the hospital. . J Stroke Cerebrovasc Dis. 1997; 6:146.

69. Rosamond W, Gorton R, Hinn A, Hohenhaus S, Morris D. Rapid response to stroke symptoms: the Delay in Accessing Stroke Healthcare (DASH) study. Acad Emerg Med 1998; 5:45-51.

70. Bratina P, Greenberg L, Pasteur W, Grotta JC. Current Emergency Department Management of Stroke in Houston, Texas. Stroke 1995; 26:409-414.

71. Fontanarosa PB, Winker MA. Timely and Appropriate Treatment of Acute Stroke: What's Missing From This Picture? JAMA 1998; 279:1307-1309.

72. MD Hammer IK, AJ Furlan, et al. Cleveland Community Experience with Intravenous Tissue Plasminogen Activator (IV-tPA): Patient Selection. 27th International Stroke Conference. San Antonio, Texas: American Stroke Association, 2002.

73. NINDS. Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke. December 12-13, 1996.

74. Lacy CR, Suh D-C, Bueno M, Kostis JB. Delay in Presentation and Evaluation for Acute Stroke: Stroke Time Registry for Outcomes Knowledge and Epidemiology (S.T.R.O.K.E.). Stroke 2001; 32:63-69.

75. Kothari R, Jauch E, Broderick J, et al. Acute Stroke: Delays to Presentation and Emergency Department Evaluation. Annals of Emergency Medicine 1999; 33:3-8.

76. Katzan IL, Sila CA, Furlan AJ, Howse DC. Community Use of Intravenous Tissue Plasminogen Activator for Acute Stroke: Results of the Brain Matters Stroke Management Survey Editorial Comment: Results of the Brain Matters Stroke Management Survey. Stroke 2001; 32:861-865.

77. Alberts MJ. tPA in acute ischemic stroke: United States experience and issues for the future. Neurology 1998; 51:S53-S55.

78. Adams HP, Jr, Adams RJ, Brott T, et al. Guidelines for the Early Management of Patients with Ischemic Stroke: A Scientific Statement From the Stroke Council of the American Stroke Association. Stroke 2003; 34:1056-1083.

79. The NINDS t-PA Stroke Study Group. Generalized Efficacy of t-PA for Acute Stroke: Subgroup Analysis of the NINDS t-PA Stroke Trial. Stroke 1997; 28:2119-2125.

80. Haley EC, Jr., Lewandowski C, Tilley BC. Myths regarding the NINDS rt-PA Stroke Trial: setting the record straight. Ann Emerg Med 1997; 30:676-82.

81. Black N LS, Petticrew M. Trends in the age and sex of patients undergoing coronary revascularization in the United Kingdom 1987-1993. British Heart Journal 1994; 72:317-320.

82. Wong CC FE, Bacchetti P, et al. Influence of gender on cardiovascular mortality in acute myocardial infarction patients with high indication for coronary angiography. Circulation 1997; 96:51-57.

83. Menon S, Pandey D, Morgenstern L. Critical factors determining access to acute stroke care. Neurology 1998; 51:427-432.

84. Alfredo M. Lopez-Yunez AB, et al. Protocol Violations in Community-Based r-tPA Stroke Treatment Are Associated with Symptomatic Intracerebral Hemorrhage. Stroke 2001; 32:12-16.

85. JM Wardlaw PD, SC Lewis et al. Can stroke physicians and neuroradiologists identify signs of early cerebral infarction on CT? J Neurology Neurosurgery Psychiatry 1999; 67:651-653.

86. Merino JG, Silver B, Wong E, Demaerschalk B, Tamayo A, Hachinski V. Physician Knowledge of the Benefits, Risks, and Contraindications of Tissue Plasminogen Activator for Acute Ischemic Stroke. Stroke 2001; 32:2208-b-2209.

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