

---

Electronic Theses and Dissertations, 2004-2019

---

2012

## Barriers To Timely Administration Of Thrombolytics In Acute Ischemic Stroke Patients

Elizabeth Joseph  
*University of Central Florida*



Part of the [Nursing Commons](#)

Find similar works at: <https://stars.library.ucf.edu/etd>

University of Central Florida Libraries <http://library.ucf.edu>

This Doctoral Dissertation (Open Access) is brought to you for free and open access by STARS. It has been accepted for inclusion in Electronic Theses and Dissertations, 2004-2019 by an authorized administrator of STARS. For more information, please contact [STARS@ucf.edu](mailto:STARS@ucf.edu).

---

### STARS Citation

Joseph, Elizabeth, "Barriers To Timely Administration Of Thrombolytics In Acute Ischemic Stroke Patients" (2012). *Electronic Theses and Dissertations, 2004-2019*. 2474.

<https://stars.library.ucf.edu/etd/2474>

BARRIERS TO TIMELY ADMINISTRATION OF THROMBOLYTICS  
IN ACUTE ISCHEMIC STROKE PATIENTS

by

ELIZABETH JOSEPH  
B.S, University of Mangalore, 1995  
M.S, University of South Florida, 2000

A thesis submitted in partial fulfillment of the requirements  
for the degree of Doctor of Nursing Practice  
in the College of Nursing  
at the University of Central Florida  
Orlando, Florida

Summer Term  
2012

Major Professor: Steven Talbert

© Elizabeth Joseph 2012

## **ABSTRACT**

Stroke is a leading cause of long term disability in the United States. The therapeutic benefits of intravenous thrombolytics is time dependent in an acute ischemic stroke patient and is an important determinant of 90 day and one year functional outcomes. This study investigated areas in the stroke alert process of a community based primary stroke care center that resulted in the delay of administration of thrombolytics within 60 minutes of an acute ischemic stroke patient's arrival to the emergency room. A retrospective descriptive design was utilized and chart reviews were done on 40 patients that received thrombolytics in the emergency room. Patient characteristics and time variables associated with the various steps in the stroke alert process were extracted. Findings showed that only 7.5% of the patients received thrombolytics within the recommended 60 minutes, with the longest time interval associated with time from arrival to the emergency room to time of evaluation by teleneurologist. There were no significant differences in the characteristics of patients who received thrombolytics within 60 minutes and those patients that received thrombolytics after 60 minutes. Recommendations were made for changes in organizational and practice strategies to improve timely administration, and for future research involving the effects of quality improvement initiatives.

## **ACKNOWLEDGMENTS**

I would like to sincerely thank and acknowledge my committee members for their time, expertise and support in helping me complete my thesis. I would like to thank Dr Ullah, for agreeing to be on my committee and taking time out of his busy schedule to help me. I would like to thank Dr Chase whose encouragement since my first class with her made me believe the end was attainable. Her guidance helped me narrow down my topic and despite all the projects she had going on, she agreed to be on my committee. Her guidance in helping me to clarify and refine my writing has been so valuable. I would like to express my sincere gratitude to Dr Talbert, my committee chair, for making the completion of this study a reality. His assistance in the statistical analysis and completion of the results has been a tremendous help. Dr Talbert's encouragement, positive feedbacks, corrections and practical attitude, I would be so ever grateful for. I would also like to acknowledge my husband for being my biggest supporter and encourager throughout the completion of my thesis and my entire study. Above all, I would like to thank God, whose unmerited favor in my life has been my strength and hope throughout my studies.

## TABLE OF CONTENTS

LIST OF FIGURES .....	vii
LIST OF TABLES .....	viii
CHAPTER 1: THE PROBLEM.....	1
Introduction .....	1
Significance .....	2
Contraindication to tPA administration .....	3
Benefits of early administration of tPA .....	3
Organizational guidelines .....	5
Purpose of the Study .....	6
Research Questions .....	6
CHAPTER 2: REVIEW OF LITERATURE .....	7
Stroke Development .....	7
Evaluation and Diagnosis of Acute Ischemic Stroke .....	8
Initial Management of Patients with Acute Ischemic Stroke .....	13
Extension of thrombolytic treatment from 3 to 4.5 hours .....	14
Intravenous thrombolytic administration.....	15
The ‘Golden Hour’ for Stroke Thrombolysis.....	16
Benefits of Early Stroke Thrombolysis.....	17
Prehospital Delays to Early Stroke Thrombolysis .....	22
Inhospital Delays to Early Stroke Thrombolysis .....	23
Summary .....	26
CHAPTER 3: METHODS .....	27
Setting.....	27
Sample Criteria and Method of Data Collection .....	27
Protection of Human Subjects.....	28
Study Design .....	28
Procedures .....	31

Statistical Analysis .....	33
CHAPTER 4: RESULTS .....	35
CHAPTER 5: DISCUSSIONS .....	44
Recommendations .....	47
Organizational Strategies.....	48
Practice Strategies.....	49
Limitations .....	54
Future Research.....	54
Summary .....	54
APPENDIX A: CRITERIA FOR PRIMARY STROKE CENTER CERTIFICATION .....	56
APPENDIX B: HEALTHCARE FACILITY INSTITUTIONAL REVIEW BOARD LETTER OF APPROVAL .....	61
LIST OF REFERENCES .....	64

## LIST OF FIGURES

Figure 1: Ischemic Stroke Alert Process.....	30
Figure 2: Number of Patients and Time Interval to tPA Administration.....	36
Figure 3: Percentages of Door to Time tPA given for the Entire Group of Patients .....	37
Figure 4: Comparison of Time to tPA Administration against severity of NIHSS score.....	40
Figure 5: Comparison of Onset of Symptoms to Door and Door to tPA Administration Time Interval .....	43



## LIST OF TABLES

Table 1: Modified Rankin Scale .....	10
Table 2: National Institute of Health Stroke Scale .....	11
Table 3 : Synthesis of Articles related to Early tPA Administration .....	18
Table 4: Sample Stroke Alert Time Log.....	29
Table 5: Threats to Validity .....	32
Table 6: Comparison of Characteristics of Ischemic Stroke Patients with Door to tPA time of Greater than 60 Minutes and those Less than 60 Minutes .....	39
Table 7: Time Intervals Associated with the Acute Stroke Alert Care Process .....	42
Table 8: Revised Stroke Alert Time Log.....	53

## **CHAPTER 1: THE PROBLEM**

### **Introduction**

Stroke is a major healthcare problem and is the leading cause of long term functional impairment in the United States, leaving 15% to 30 % of its victims permanently disabled and approximately 20% still requiring rehabilitative care at 3 months post stroke (Roger, Go, Lloyd-Jones, Adams, et al., 2011). With someone suffering from a stroke every 40 seconds (American Heart Association, 2010), its impact on health and the economy is staggering. It is estimated that 795,000 individuals suffer from a first time stroke or a recurrence each year, with a current stroke survivor membership of 6.4 million Americans (Roger, Go, Lloyd-Jones, Adams, et al., 2011). Stroke is not only a sudden life altering event in the life of a stroke patient, but it also leaves a heavy toll on family members and care givers. In a survey of preferences of persons at an increased risk of stroke, greater than 45% of the participants considered stroke to be a worse outcome than death (Samsa, Matchar, Goldstein, Bonito, et al., 1998). Moreover, the economic impact is devastating with loss of earning being the biggest cost contributor, with a total projected cost of stroke between 2005 to 2050 estimated to be \$1.52 trillion for whites, \$379 billion for blacks, and \$313 billion for Hispanics (Brown, Boden-Albala, Langa et al., 2006). In 2010, the cost of stroke care, both direct and indirect costs, was \$73.7 billion (Roger, Go, Lloyd-Jones, Adams, et al., 2011).

Mortality data released in 2008 revealed that stroke had declined from being the third leading cause of death in the United States to the fourth leading cause of death, after heart disease, cancer and chronic lower respiratory diseases (Center for Disease Control and Prevention [CDC], 2011). Though this statistic is an important reduction signifying the efforts

and progress in the prevention and treatment of cerebrovascular diseases, the need to reduce the burden of post stroke disability with its incalculable human cost and surmounting economic costs remains (Towfighi & Saver, 2011).

## **Significance**

Strokes primarily fall into three main categories, with ischemic strokes accounting for 87% of all strokes, intracerebral hemorrhage for 10% and subarachnoid hemorrhage strokes for 3% (Roger, Go, Lloyd-Jones, Adams, et al., 2011). Depending on the extent of brain damage, individuals suffering from stroke can experience altered skills of perception, sensation, intellect and movement, skills that they have mastered over a lifetime. The main treatment objective for an individual who has suffered an ischemic stroke is to reinstate the cerebral blood flow as quickly as possible after an arterial occlusion, in order to decrease damage to viable brain tissue.

The use of intravenous recombinant tissue plasminogen activator (tPA) has revolutionized acute ischemic stroke treatment and remains the first line choice of therapy. It is the only approved drug by the Food and Drug Administration (FDA) for the treating acute ischemic stroke (Adams, del Zoppo, Alberts, Bhatt, et al., 2007). However, tPA benefits diminish with each passing hour after initial stroke symptoms. Improved outcomes have been observed if tPA is administered within the first three hours of stroke onset (Adams, del Zoppo, Alberts, Bhatt, et al., 2007). After completing a systematic review of current studies, a scientific advisory statement was issued by the American Heart Association and American Stroke Association (AHA/ASA) recommending the use of tPA up to 4.5 hours from the initial onset of symptoms of an acute ischemic stroke, for eligible patients without contraindications (Del

Zoppo, Saver, Jauch, & Adams, 2009). The evidence clearly states that early tPA administration is imperative.

### **Contraindication to tPA administration**

Some of the absolute contraindication to tPA administration include uncontrolled systolic blood pressure greater than 185 mm HG or diastolic blood pressure greater than 110 mm Hg in spite of repeated treatment, acute trauma or active bleeding, an arterial puncture at an incompressible site within the past week, clinical presentation suggesting subarachnoid hemorrhage, seizure with postictal neurological impairment, platelet count less than 100,000/mm<sup>3</sup>, prothrombin time of greater than 15, known arteriovenous malformation, head trauma or stroke in the previous three months, and surgery in the past two weeks (Rivera-Bou, Cabanas, & Villanueva, 2011; Adams, del Zoppo, Alberts, Bhatt, et al., 2007). In order to be eligible for tPA administration, the neurological signs should not be minor, isolated, nor should it clear spontaneously (Adams, del Zoppo, Alberts, Bhatt, et al., 2007).

### **Benefits of early administration of tPA**

Ischemic stroke is a treatable neuroemergency, but every minute of delayed therapy may have adverse consequences. This was emphasized by the American Stroke Association in their slogan, “Time lost is brain lost”. Using quantitative neurosterology and stroke neuroimaging, Saver (2006) calculated the amount of brain lost per unit time during an acute ischemic stroke. During the evolution of an average non lacunar ischemic stroke (10 hours), every untreated minute of a large vessel ischemic stroke results in the loss of 7 miles of axonal fibers, 1.9 million neurons, and 13.8 billion synapses (Saver, 2006).

The therapeutic benefits of tPA decreases with time, with no significant benefit identified after 4.5 hours from the onset of symptoms of an acute ischemic stroke. An analysis of data from six large randomized tPA trials showed a strong association between early treatment and favorable functional outcome (Hacke, Donnan, Fieschi, Kaste, et al., 2004). The odds of a favorable 3 month outcome increased as onset of stroke to treatment time decreased ( $p=0.005$ ). The odds ratio of a favorable outcome for patients treated with tPA within 90 minutes when compared with controls was 2.81 (1.75–4.50) and was 1.55 (1.12–2.15) for those treated within 91 to 180 minutes (Hacke, Donnan, Fieschi, Kaste, et al., 2004). The National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study showed that patients treated within 90 minutes from ischemic stroke onset have an increased odds of improvement at 24 hours and a favorable functional outcome at 3 months when compared to patients treated from 91 minutes to 180 minutes after the onset of stroke (Marler, Tilley, Lu, Brott, et al., 2000). The adjusted OR (95% CI) for a favorable 3 month outcome associated with tPA was 2.11 (1.33 to 3.35) within 90 minutes and 1.69 (1.09 to 2.62) when given between 91 to 180 minutes.

Analysis of pooled data from six major intravenous tPA stroke trials showed that tPA therapy was associated with more benefit than harm up to 4.5 hours after onset of ischemic stroke and there was no net benefit when administered between the 4.5 and 6 hour time after stroke onset (Lansberg, Schrooten, Bluhmki, Thijs, & Saver, 2009). This large pooled analysis showed the number needed to treat for benefit was 3.6 for patients treated between 0 and 90 minutes, 4.3 with tPA administration between 91 and 180 minutes, 5.9 with tPA administration between 181 and 270 minutes, and 19.3 between 271 and 360 minutes. The estimates for number needed to treat for harm for the corresponding time frames were 65, 38, 30, and 14 respectively

(Lansberg, Schrooten, Bluhmki, Thijs, & Saver, 2009). Furthermore, patients with door-to-needle time for administration of intravenous tPA of less than 60 minutes had less frequent intracranial hemorrhage, and lower in-hospital mortality when compared to patients with greater than 60 minutes door-to-needle time (Fonarow, Smith, Saver, Reeves, et al., 2011). In fact, every reduction in door-to-needle time of 15 minutes was associated with a 5% decrease for in-hospital mortality (adjusted odds ratio of 0.95: 0.92 to 0.98; P = 0.0007).

### **Organizational guidelines**

Evidence from these trials has been transformed into recommendations from several national, international, and accrediting organizations. The AHA/ASA guidelines has set the target for primary stroke center of a door-to-needle time of within 60 minutes of patient's arrival to the emergency room with onset of stroke symptoms (Adams, del Zoppo, Alberts, Bhatt, et al., 2007). The NINDS national symposium on the rapid identification and treatment of acute ischemic stroke calls for a door-to-needle time of within an hour of patient's presentation to the emergency room (Furlan, 1997). The Joint Commission requires primary stroke care centers to administer tPA within 60 minutes of an ischemic stroke patient's arrival to the emergency room, in at least 80% of the cases (Joint Commission, 2011).

Despite the evidence and recommendations, the door-to-needle time in accredited stroke centers varies. An analysis of 25,504 ischemic stroke patients that were treated with tPA in 1082 Get With the Guidelines-Stroke (GWTS-Stroke) hospitals revealed a median door-to-needle time of 78 minutes, with less than one third of the patients who arrive within three hours of stroke symptom onset having a door-to-needle time of less than 60 minutes (Fonarow, Smith, Saver, Reeves, et al., 2011). Another study evaluated data from 57 academic and community centers in

the United States found the median time from stroke onset to treatment was 2 hours 44 minutes with an average door-to-needle time of 96 minutes (Albers, Bates, Clark, Bell, Verro, & Hamilton, 2000). Hence, the need remains to identify hindrances in the stroke care processes of primary stroke centers that delay timely administration to tPA to achieve the maximum neurological improvement in the stroke patients.

### **Purpose of the Study**

The purpose of this study is to identify the areas in the stroke alert care process within a community based primary stroke center, that delay the administration of tPA within 60 minutes of an eligible ischemic stroke patient's arrival to the emergency room.

### **Research Questions**

What are the in-hospital factors that increase time to administration of tissue plasminogen activator in stroke patients who seek medical attention within the critical four hour window and who qualify for the treatment?

Do patients who have times to administration of tPA greater than 60 minutes differ significantly from patients who have times equal to or less than 60 minutes?

## **CHAPTER 2: REVIEW OF LITERATURE**

### **Stroke Development**

Stroke occurs as a result of interruption to the cerebral blood flow, causing extensive changes in cellular homeostasis. Approximately 70 % of the strokes are ischemic in nature, and 15% are hemorrhagic. The absence of extravasated blood in the brain parenchyma is what differentiates ischemic stroke from hemorrhagic stroke (Zivin, 2011). Though some blood flow to the ischemic brain is maintained by collateral circulation, the critical supply of oxygen and glucose necessary for normal brain function is impaired during a stroke (Crocco, Tadross, & Kothari, 2009). The average rate of cerebral blood flow is 40 to 60 ml/100g of brain per minute. When this level drops to 15 to 18ml/100g of brain, the brain begins to lose its electrical activity. Further drops in cerebral blood flow results in brain cell death. The most common disorder that leads to a stroke is atherosclerosis. Often, a thrombus can form on the atherosclerotic plaque, which eventually breaks off and flows into the blood stream, leading to obstruction of blood flow (Zivin, 2011).

The clinical manifestations of stroke depend on the artery or blood vessel that is occluded and are as follows (Crocco, Tadross, & Kothari, 2009):

- Middle cerebral artery occlusion causes symptoms such as contralateral hemiparesis, sensory loss mainly of arm and face, contralateral inferior quadrantanopsia, expressive aphasia or anosognosia and spatial disorientation.
- Anterior cerebral artery occlusion causes contralateral hemiparesis, and sensory loss that is worse in leg.



- Posterior cerebral artery occlusion causes memory impairment, contralateral homonymous hemianopia or superior quadrantanopia.
- Superior cerebral artery occlusion causes gait disturbance, gaze paresis, contralateral hemiparesis, somnolence, nausea, dizziness, headache progressing to ipsilateral hemiataxia, dysarthria.
- Basilar artery occlusion causes sensory loss, contralateral hemiparesis, or cerebellar signs.
- Basilar apex occlusion causes amnesia and bilateral blindness
- Internal carotid artery occlusion causes symptoms associated with middle cerebral artery and ipsilateral blindness.

The survival of neurons in an ischemic stroke is influenced by the duration of occlusion; with prolonged occlusion causing an increase in cerebral infarction as well as irreversibility of neurological deficits (Crocco, Tadross, & Kothari, 2009). Hence the critical need to recanalize the occluded artery and reperfuse the ischemic areas of brain with thrombolytics such as tissue plasminogen activator (tPA) within the narrow treatment window is of paramount importance.

### **Evaluation and Diagnosis of Acute Ischemic Stroke**

Regardless of the severity of stroke symptoms, patients who present with stroke type symptoms should be treated with the same urgency as a patient who presents with acute myocardial infarction or a severe trauma (Adams, del Zoppo, Alberts, Bhatt, Brass, et al., 2007). Hospitals should have efficient pathways and processes in place to evaluate potential stroke patients. There should be simultaneous notification of stroke team and implementation of stroke

care pathways while evaluation of the potential stroke patient is going on in the emergency department. Initial evaluation during the initial diagnosis of acute ischemic stroke includes:

***History and physical examination:*** The single most important piece of history is the timing of symptom onset as this determines the eligibility for thrombolytic treatment. For patients who cannot speak or wakes up with stroke symptoms, the time of onset reverts back to the time when they were last seen in a normal condition (Adams, del Zoppo, Alberts, Bhatt, Brass, et al., 2007). It is also important to ask other questions that pertain to the eligibility of tPA such as current use of anticoagulants. Conditions or symptoms that mimic stroke should be considered such as conversion disorder, hypoglycemia, seizures, complicated migraines and hypertensive encephalopathies. A complete and thorough physical examination should continue through from the initial assessment of airway, breathing and circulation.

***Neurological examination and stroke scale scores:*** The emergency department physician's neurological assessment should be brief and thorough. This usually precedes the examination by the neurologist on call. The use of standardized stroke scales such as national institute of health stroke scale (NIHSS) or the modified Rankin scale further enhances the examination. The modified Rankin scale (Table 1) is a simplified overall assessment of function that extends from no disability (score of 0) to severe disability (score of 5). The NIHSS (Table 2) is a 42 point scale that has 11 categories of neurological deficits. These scales help to identify the possible location of vessel occlusion, quantify the degree of neurologic deficit and identify patient's eligibility for various interventions (Adams, del Zoppo, Alberts, Bhatt, Brass, et al., 2007).

**Table 1: Modified Rankin Scale**

<b>Score</b>	<b>Description</b>
<b>0</b>	No symptoms at all
<b>1</b>	No significant disability despite symptoms; able to carry out usual activities and duties
<b>2</b>	Slight disability; unable to carry out all previous activity, but able to manage affairs without assistance
<b>3</b>	Moderate disability, requiring some help, but able to walk without assistance
<b>4</b>	Moderately severe disability; unable to walk or attend to physical needs without assistance
<b>5</b>	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
<b>6</b>	Death

Note. Adapted from “Interobserver agreement for the assessment of handicap in stroke patients”, by J.C. Van Swieten, P. J. Koudstaa, M. C. Visser, et al., 1988, *Stroke*, 19, p.604

**Table 2: National Institute of Health Stroke Scale**

Item	Score
1a. Level of consciousness	0 = Alert and responsive 1 = Arousable to minor stimulation 2 = Arousable only to painful stimulation 3 = Unarousable or reflex responses
1b. Questions Ask patient's age and month. Must be exact	0 = Both correct 1 = One correct 2 = Neither correct
1c. Commands Ask patient to open/close eyes, grip and release non-paretic hand.	0 = Both correct 1 = One correct 2 = Neither correct
2. Best gaze Horizontal extra ocular movements by voluntary or reflexive (oculocephalic maneuver) testing.	0 = Normal 1 = Partial gaze palsy; abnormal gaze in one or both eye 2 = Forced eye deviation or total paresis which cannot be overcome by oculocephalic maneuver
3. Visual fields Test by confrontation or threat as appropriate. If monocular, score field of good eye.	0 = Normal 1 = Partial hemianopia, quadrantanopia, extinction 2 = Complete hemianopia 3 = Bilateral hemianopia or blindness
4. Facial palsy If stuporous, check symmetry of grimace to pain. Paralysis (lower face).  5a. Left motor arm 5b. Right motor arm Arms outstretched 90° (if patient is sitting or 45° (if supine) for 10 seconds. Encourage best effort, note paretic side.  6a. Left motor leg 6b. Right motor leg Raise leg to 30° (always test patient supine) for 5 seconds.	0 = Normal 1 = Minor paralysis (normal looking face, asymmetric smile) 2 = Partial paralysis 3 = Complete paralysis (upper and lower face) 0 = No drift 1 = Drift but does not hit bed 2 = Some antigravity effort, but cannot sustain 3 = No antigravity effort, but minimal movement present 4 = No movement at all X = Unable to assess due to amputation, fusion, etc.
7. Limb ataxia Check finger-nose-finger; heel-shin; score only if out of proportion to weakness.	0 = No ataxia (or aphasic, hemiplegic) 1 = Ataxia present in one limb 2 = Ataxia present in two limbs X = Unable to assess as above

Item	Score
8. Sensory Use safety pin. Check grimace or withdrawal if stuporous. Score only stroke related losses.	0 = Normal 1 = Mild to moderate unilateral sensory loss but patient aware of touch. 2 = Severe to total sensory loss, patient unaware of touch (or bilateral sensory loss or comatose)
9. Best language Ask patient to describe cookie jar picture, name objects, read sentences. May use repeating, writing, stereognosis.	0 = Normal 1 = Mild-moderate aphasia 2 = Severe aphasia(almost no information exchanged) 3 = Mute, global aphasia, or coma
10. Dysarthria Ask patient to read or repeat a list of words.	0 = Normal 1 = Mild-moderate dysarthria 2 = Severe, unintelligible or mute 3 = Severe, unintelligible or mute X = Intubation or mechanical barrier
11. Extinction and inattention Simultaneously touch patient on both hands, show fingers in both visual fields, ask patient to describe deficit, left hand.	0 = Normal, none detected (or severe visual loss with normal cutaneous responses) 1 = Neglects or extinguishes to bilateral simultaneous stimulation in any sensory modality ( visual, tactile, auditory, spatial, or personal inattention) 2 = Profound hemi-inattention or extinction in more than one modality

Note. Adapted from *National Institute of Health Stroke Scale (NIHSS)*, by National Institute of Health, Retrieved Oct 1, 2011 from [www.ninds.nih.gov/doctors/NIH\\_Stroke\\_Scale\\_Booklet.pdf](http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale_Booklet.pdf)

**Diagnostic tests:** Some of the initial diagnostic tests done to aid with the diagnosis of stroke and rule out other causes are complete blood count, blood glucose, comprehensive metabolic profile, prothrombin time, activated partial thromboplastin time and international normalized ratio. All patients should also have a non contrast brain CT to rule out hemorrhage. Since cardiac abnormalities are common among stroke patients, cardiac enzymes, 12 lead electrocardiogram and a clinical cardiovascular examination should be completed (Adams, del Zoppo, Alberts, Bhatt, Brass, et al., 2007).

The number of diagnostic tests performed initially on the stroke patient should be limited due to the critical time factor, with history taking and neurological examination remaining the cornerstone of diagnostic evaluation.

### **Initial Management of Patients with Acute Ischemic Stroke**

The need to maintain medical stability and salvage ischemic brain tissue that is not already infarcting, remains the primary goal during the initial phase of management (Oliveira-Filho & Samuels, 2011). Restoration of blood flow is achieved from the utilization of thrombolytic therapy, which has a narrow therapeutic time frame. The US Food and Drug Administration approved the use of intravenous recombinant tissue plasminogen activator (tPA) in 1996, for use within 3 hours of stroke onset (Adams, del Zoppo, Alberts, Bhatt, Brass, et al., 2007). This approval was based on the results of the clinical trials conducted by the National Institute of Neurological Disorders and Stroke (NINDS).

The NINDS (1995) study randomly enrolled 624 patients into treatment with intravenous tPA vs placebo, within 3 hours of stroke onset. Patients had to meet multiple strict criteria to be enrolled in the study, which included no evidence of hemorrhage on scan, no prior stroke or

trauma within prior 3 months, no surgery within 14 days, no arterial puncture within 7 days, no recent use of anticoagulants, no gastrointestinal or urinary tract bleed within 21 days, had rapidly improving symptoms, or had seizure at the time of stroke onset. Despite an increased incidence of symptomatic intracerebral hemorrhage in the treatment group, patients in the tPA intervention group within 3 hours of stroke onset, had improved clinical outcome at 3 months and were 30% more likely to have minimal or no disability at 3 months compared to the placebo group (NINDS, 1995).

In order to further assess the safety profile and clinical outcomes associated with intravenous tPA use, a phase 4 study known as the Standard Treatment with Alteplase to Reverse Stroke (STARS) study, was mandated by FDA. This prospective study enrolled 389 patients treated at 57 hospitals and followed their clinical course post tPA intervention for acute ischemic stroke. The results demonstrated good clinical outcome at 30 days, with approximately 43% of patients being functionally independent. Lower rates of intracerebral hemorrhage were also noted when compared to the NINDS study (Albers, Bates, Clark, Bell, Verro, & Hamilton, 2000).

### **Extension of thrombolytic treatment from 3 to 4.5 hours**

The European Cooperative Acute Stroke Study (ECASS III) investigators conducted their third clinical trial to test the efficacy and safety of tPA treatment between 3 to 4.5 hours. A total of 821 patients were randomized to the treatment and placebo group. This was a double blinded, parallel group trial. Results demonstrated a modest but significant improvement in the clinical outcome of patient who received tPA between 3 to 4.5 hours as evidenced by a modified Rankin score of 1 or less (Hacke, Kaste, Bluhmki, Brozman, Dávalos, et al., 2007). The rate of intracranial hemorrhage was higher in the treatment group than with the placebo group as noted

with other studies. However, mortality between the two groups did not show a significant difference. Unlike the NINDS trial, patients with severe strokes were excluded from this trial. This could be the possible explanation of improved outcomes in both placebo and treatment groups of the ECASS III trial, as patients enrolled had initial milder severity of stroke symptoms.

### **Intravenous thrombolytic administration**

Prior to administration of intravenous tPA, it is necessary to ensure that the patient is within the recommended time window, from the initial onset of stroke symptoms. The eligibility criteria, dosing of tPA and monitoring after and during administration of tPA are discussed below.

***Eligibility criteria:*** The clinical diagnosis of ischemic stroke must be made with measurable neurologic deficit (Oliveira-Filho , & Samuels, 2011). The patient should have had a non hemorrhagic stroke as determined by the CT scan. The CT scan should not show evidence of a multilobar infarction with hypodensity involving greater than 33 % of cerebral hemisphere, in order to be eligible for tPA.

***Dosing:*** The dose of tPA is calculated at 0.9 mg/kg of actual body weight, with a maximum dose of 90 mg. An initial bolus of 10 % of the total dose is given over one minute, followed an infusion of the remainder dose over one hour (Oliveira-Filho, & Samuels, 2011).

***Monitoring:*** Vital signs and neurological checks must be monitored every 15 minutes for 2 hours, then every 30 minutes for six hours and then hourly for 24 hours. Invasive procedures and use of anticoagulant or antiplatelet drugs must be avoided. During the first 24 hours blood



pressure must be maintained below a systolic of 180 mm Hg and diastolic of 105 mm Hg (Oliveira-Filho , & Samuels, 2011).

### **The ‘Golden Hour’ for Stroke Thrombolysis**

The average duration of an acute ischemic infarct from onset to completion differs widely from patient to patient. For a non lacunar stroke, the duration of evolution may extend from 8 to 12 hours (Saver, 2006). The individual differences is influenced by location of vessel occlusion, level of ischemic preconditioning, levels of collaterals, and several other factors including blood sugar, blood pressure and volume of blood (Kidwell, Alger, & Saver, 2003). Using modern quantitative neurosterology, an average human brain is estimated to have approximately 130 billion neurons (Saver, 2006).

Utilizing quantitative estimates of the rate of neural circuitry loss in an acute ischemic stroke, investigators were able to predict the rate of neuron loss. Patients experiencing a large vessel ischemic stroke loses 1.9 million neurons, 14 billion synapses and 7.5 miles of myelinated fiber every minute. That translates to 32,000 neurons, 230million synapses and 200 meter of myelinated fibers every second of an acute ischemic event. The brain ends up losing as many neurons as it would have in 3.6 years of normal aging, for every hour of a stroke where treatment is delayed (Saver, 2006).

A pooled analysis of six major randomized clinical trials of acute stroke using intravenous tPA was conducted to calculate time specific number needed to treat estimates over the entire range of clinically relevant functional outcomes. Patients were divided into four main time categories, each consisting of a 90 minute treatment time window. The time categories were

0 to 90 minutes, 91 to 180 minutes, 181-270 minutes and 271 to 360 minutes. The analysis revealed a progressive increase in number needed to treat to benefit with intravenous tPA with longer treatment time windows and a progressive decrease in number needed to treat to harm with longer treatment time windows (Lansberg, Schrooten, Bluhmki, Thijs, & Saver, 2009). Every 10 minute delay in starting a tPA infusion among 100 tPA eligible patients resulted one less patient having an improved disability outcome (Lansberg, Schrooten, Bluhmki, Thijs, & Saver, 2009).

These findings further emphasizes the need for emergent care during an acute ischemic stroke as human nervous tissue is irretrievably lost, resulting in lifelong disability and poor functional outcomes.

### **Benefits of Early Stroke Thrombolysis**

In an acute ischemic stroke, the benefits of tPA administration is strongly time dependent, with the greatest therapeutic benefit being achieved early on after symptom onset and gradually declines with time. Early administration of tPA have been associated with lower mortality and greater neurological improvement, as demonstrated by the studies described below.

**Table 3 : Synthesis of Articles related to Early tPA Administration**

Primary Study	Sample and Settings	Characteristics of Interventions	Results	Benefits of Early Administration	Limitations
<p>Fonarow, Smith, et al., 2011</p>	<p>Retrospective review of data from acute ischemic stroke patients treated with tPA within 3 hours of symptom onset in 1082 hospitals participating in the Get With the Guidelines–Stroke Program from April 1, 2003, to September 30, 2009. Total sample was 25,504 patients.</p> <p>Goal was to determine frequency, patient and hospital characteristics, and temporal trends in patients treated with door-to-needle times <math>\geq 60</math> minutes.</p>	<p>No direct intervention.</p> <p>Consecutive patients admitted with the principal clinical diagnosis of acute stroke or TIA by prospective clinical identification, retrospective identification through the use of discharge codes, or a combination. Abstracted data included demographics, medical history, onset time of stroke symptoms (recorded as last known well time), arrival time, in-hospital diagnostic studies, treatments and procedures, discharge treatments and counseling, tPA treatment initiation time, tPA complications, in-hospital mortality, and discharge destination.</p>	<p>Door-to-needle times of <math>\leq 60</math> minutes was documents in 26.6% of sample (6,790 of 25,504)</p> <p>Patient Characteristics of Door-to-needle times of <math>\leq 60</math> minutes:            Younger (68.9 years vs. 70.1 years , <math>p&lt;0.0001</math>)            Male (54.0% vs. 49.7%, <math>p&lt;0.0001</math>)            White (77.0% vs. 75.7%, <math>p=0.0115</math>)            EMS transport (85.9% vs. 84.2%, <math>p&lt;0.0001</math>)</p> <p>Hospital Characteristics of Door-to-needle times of <math>\leq 60</math> minutes:            Shorter median time from arrival to CT (18 vs. 24 mins, <math>p&lt;0.0001</math>)            Time from arrival to CT <math>\leq 25</math> mins (68.5 vs. 53%, <math>p&lt;0.0001</math>)            Higher volume of tPA administration 20+ patients (23.5 vs. 15.4, <math>p&lt;0.0001</math>)            TJC Primary Stroke Center (68.5% vs. 65.9%, <math>p&lt;0.0001</math>)            Arrival “on hours” (OR=1.27; 95% CI: 1.18 to 1.37)</p>	<p>Inpatient case fatality rate lower (8.6% vs. 10.4%, <math>p=0.0001</math>)            Rates of intracranial hemorrhage within 36 hours were lower (4.7% vs. 5.6%, <math>p=0.002</math>)            Odds of mortality was 5% lower with every 15-minute reduction in door-to-needle time (OR= 0.95; 95% CI: 0.92 to 0.98)</p>	<p>Data used in this was only from major large teaching hospitals</p>

<b>Primary Study</b>	<b>Sample and Settings</b>	<b>Characteristics of Interventions</b>	<b>Results</b>	<b>Benefits of Early Administration</b>	<b>Limitation</b>
<p>Hacke, Donnan, et al., 2004</p>	<p>Pooled analysis of common data elements from six randomized placebo-controlled trials using tPA.</p> <p>Total of 2775 patients treated at more than 300 hospitals in 18 countries.</p> <p>Goal was to determine whether time-to-treatment with intravenous thrombolytic therapy is a critical predictor of therapeutic benefit.</p>	<p>No direct intervention.</p> <p>Patients from six major trials with similar strict inclusion and exclusion criteria for enrollment and administration of tPA. Similar outcome measures were utilized such as NIHSS, modified Rankin Scale, and Barthel Index up to 3 months after stroke onset, calculated mortality, occurrence of hemorrhage with CT, and clinical scales for their primary outcome measures.</p>	<p>Median age was 68 years, 84.6% were reported as white, 9.1% as black, 2.0% as Hispanic.</p> <p>Median baseline NIHSS score was 11, and median onset to treatment of 243 minutes. 1847 patients (67%) were treated for longer than 3 h after symptom onset.</p>	<p>Improved functional outcomes with early tPA; for 0 to 90 minutes (OR= 2.8, 95% CI: 1.8 to 4.5), for 91 to 180 minutes (OR=1.6, 95% CI: 1.1 to 2.2), for 181 to 270 minutes (OR=1.4, 95% CI: 1.1 to 1.9), and for 271 to 360 minutes (OR = 1.2, 95% CI: 0.9 to 1.5).</p> <p>Mortality rates lower in those treated within 0-90 minutes when compared to others (0.88, 95%: 0.54–1.46).</p>	<p>Differences in trial methodologies</p>

<b>Primary Study</b>	<b>Sample and Settings</b>	<b>Characteristics of Interventions</b>	<b>Results</b>	<b>Benefits of Early Administration</b>	<b>Limitations</b>
Marler, Tilley, et al., 2000)	Retrospective review of data from two major tPA stroke trials conducted at eight centers using over 40 hospitals. A total of 622 patients were included in the study. Goal was to analyze the relationship of onset-to-treatment time to outcome at 3 months, early improvement at 24 hours, and intracranial hemorrhage within 36 hours.	No direct intervention. The NINDS rt-PA Stroke Study was performed in two parts, each of which was a separate trial. The two parts differed only in the prospectively defined primary outcome. Data from both parts of the study were combined for analyses to obtain more statistical power and a more complete picture of the effect of onset to treatment time on patient outcomes. A favorable outcome was defined as recovery with minimal or no deficit 3 months after treatment using four outcome measures: the Barthel Index , modified Rankin Scale, Glasgow Outcome Scale, and NIHSS score.	Onset of time to treatment in between 0 to 90 vs. 91 to 180 minutes, 86 vs. 153 minutes. Delay from admission to treatment 53 vs. 84.7 mins.	Improved functional outcome at 24 hours: for 0 to 90 minutes (OR = 1.71, 95% CI: 1.09 to 2.70) and for 91 to 180 minutes (OR= 1.12, 95% CI: 0.71 to 1.76). An OR > 1 indicates that the odds of a four or more point NIHSS improvement at 24 hours in tPA treated patients when compared to placebo.  Favorable clinical outcome at 3 months: for 0 to 90 minutes (OR = 2.53, 95% CI: 1.53 to 4.19), for the 91 to 180 minutes (OR = 1.61, 95% CI: 1.02 to 2.55).	Baseline NIHSS is a good predictor of outcome, however, there was an imbalance in the NIHSS severity of stroke randomized in the two treatment groups at different onset to treatment time.

<b>Primary Study</b>	<b>Sample and Settings</b>	<b>Characteristics of Interventions</b>	<b>Results</b>	<b>Benefits of Early Administration</b>	<b>Limitations</b>
Strbian, Soinne, et al., 2010	Single-center assessment of the A total of 878 patients with ischemic stroke received thrombolysis within 4.5 hours from the symptom onset, between January 2003, and December 2008. Purpose was to identify effect of ultra-early thrombolysis on patient outcomes.	No direct intervention. All patients were prospectively included in the study, that is, all consecutive patients considered eligible for stroke thrombolysis and treated within the time window of 4.5 hours from symptom onset .	Median age was 70.5 years, 399 (45.4%) females. Median baseline NIHSS was 9. Median onset to treatment time (OTT) was 115 minutes. 257 (29%) had OTT < 90 minutes and 87 (10%) had OTT < 70 minutes.	Improved favorable outcome for < 70minutes OTT when compared to > 90 minutes, after adjusting for baseline stroke severity based on NIHSS. Specifically, for the patients with NIHSS 7 to 12 (OR =5.15, 95% CI: 1.50 to 27.5) and for those with NIHSS > 13 (OR= 2.74, 95% CI:1.26 to 5.90). Of the patients with OTT >90 minutes, those with NIHSS 7 to 12 had an OR of 1.72 (1.00 to 2.96) for a favorable outcome, and those with NIHSS >13 had lower mortality than the ones with OTT > 90 minutes (16.4% versus 29.5%).	

## **Prehospital Delays to Early Stroke Thrombolysis**

Although the benefits of early stroke thrombolysis and timely administration of tPA have been demonstrated, only a small amount of patients actually receive thrombolytic treatment (Schestatsky & Picon, 2005). This has been attributed to the delays that are encountered along the patient pathway; along with the narrow time window of 3 hours for effective thrombolytic therapy (Dirks, Niessen, Huijsman, van Wijngaarden, et al., 2007).

A systematic review of literature was conducted to identify barriers to the administration of tPA for acute stroke. All prospective and retrospective observational studies that addressed the duration and nature of barriers and delays to thrombolysis from 1990 to 2001 were retrieved (Kwan, Hand, & Sandercock, 2004). Publications that were opinions, not original research, studies of specialized groups of stroke patients and studies that only looked at patients who received tPA were excluded from the analysis. Of the 54 studies included in the review, majority reported a mean delay time of 2 to 6 hours from stroke onset to arrival to the hospital. Another systematic review was conducted on literature published between 1995 to 2009 to identify barriers to thrombolytic therapy (Johnson, & Bakas, 2010). Based on these two reviews, the three major prehospital factors that negatively influenced the timely arrival to hospital and the administration of tPA were:

1. Patient or family knowledge deficit regarding stroke symptoms and acuity: This category included factors such patients living by themselves, lack of witness when stroke symptoms occurred, patient's refusal to go to hospital, lack of recognition of stroke symptoms by patient or family, and lack of urgency on the part of patient or family to seek help once symptoms developed;

2. Non emergent mode of arrival: This delay occurred when patients did not call for an ambulance or attempted to call their primary care provider first to discuss their symptoms. Patients with more severe stroke symptoms, hemorrhagic stroke patients, older patients, and patients with witnessed stroke were more likely to call for an ambulance and hence have shorter delay in arriving at the hospital; and
3. Delay in emergency medical personnel services: This included delay in timely arrival of ambulance, delay in ambulance arrival at the patient to reaching the hospital or triage of stroke patients as non urgent by emergency medical personnel (Johnson, & Bakas, 2010; Kwan, Hand, & Sandercock, 2004).

### **Inhospital Delays to Early Stroke Thrombolysis**

Though delayed presentation to the emergency room after the onset of stroke symptoms has been identified as the major limiting factor to utilization of tPA, several inhospital factors have also been identified. In fact, those patients who arrived very early on after the onset of stroke symptoms had a longer arrival to treatment time. For every 30 minute delay between onset of stroke symptoms and arrival to the emergency room, there was an associated 15 minute decrease in time between arrival and administration of tPA (Albers, Bates, Clark, Bell, et al., 2000).

In an Austrian study, data was prospectively collected on all admitted stroke patients using standardized variable definitions and scores (Ferrari, Knoflach, Kiechl, Willeit, et al., 2010). Of the 3287 patients who received intravenous thrombolysis, 2663 patients were included in the analysis. Patients with unknown stroke onset to arrival time and those patients with door to



treatment time of greater than 240 minutes were excluded from the study. After multivariate adjustments and even after controlling confounding variables such as stroke severity, weekend admissions, age, gender, transportation to and within the hospitals, and imaging modality, the findings were significant. Patients who arrived within 60 minutes had a longer door to treatment time when compared to patients who arrived between 61 to 120 minutes and 121 to 180 minutes after stroke onset, whose door to treatment time were 6.9 minutes and 13.9 minutes shorter, respectively ( $p < 0.001$ ).

A similar retrospective chart analysis was conducted on a smaller scale at an US academic medical center involving 31 patients. An inverse relationship between early arrival to hospital and tPA administration time was discovered (Romano, Muller, Merino, et al., 2007). Investigators of both the above mentioned studies make the assumption that this delay may be related to the decreased sense of perceived urgency when patients arrive early on after stroke onset. The feeling of 'having more time' may produce small delays in different levels of patient care and management.

Systematic review of literature further identified inhospital factors that act as barriers to timely administration of tPA (Johnson, & Bakas, 2010; Kwan, Hand, & Sandercock, 2004). Specific factors causing inhospital delay to the delivery of thrombolysis identified in these reviews included:

- Delay in medical assessment: This may be related to incorrect triaging of a stroke emergency and thereby delay in alerting the acute stroke team, delay in initial medical assessment, and delay in neurologist's assessment.

- Delay in neuroimaging: This delay occurred due to late order entry for scan, delay in transporting the patient to radiology department, delay in scanning in patient and reporting of the results by the radiologist. Major organizational changes such as relocating computerized tomography (CT) scanner to the emergency room, prenotification by emergency medical personnel and development of a stroke team was able to reduce delays related to CT by 1 hour and reduce door to treatment time by 38 minutes (Lindsberg, Häppölä, Kallela, Valanne, Kuisma, & Kaste, 2006).
- Delay in obtaining consent for thrombolysis: This delay occurs from difficulty in obtaining consent from patients due to their decreased level of consciousness or speech impairment associated with acute ischemic stroke. The lack of a standardized protocol for capacity assessment in acute ischemic stroke further adds to this delay (White-Bateman, Schumacher, Sacco, & Appelbaum, 2007).
- Delay from physician uncertainty regarding treatment with tPA: This delay arises from physician uncertainty regarding diagnosis of acute stroke, difficulty in initiating treatment within 3 hours and reluctance in starting tPA due to lack of confidence in tPA treatment or trial results.
- Delay from inefficient process of emergency stroke care. This delay has been attributed from delays in assessment, transfers and lack of collaboration. The lack of an expedited stroke triage pathway involving close collaboration between emergency personnel, emergency physicians, nurses, neurologist, and radiologist, can further contribute to inhospital delay (Lau, Soo, Graham, Woo, et al., 2010).

- Delay from other barriers: These include delay in transfer of a patient from a non stroke center, delay in obtaining or retrieving prior records, delay in obtaining drug from the pharmacy, delay in performing phlebotomy, inadequate training of emergency room physicians, and low level of accuracy of stroke diagnosis by emergency medical personnel.

### **Summary**

This chapter discusses the benefits and need for emergent care and treatment of an acute ischemic stroke patient. Research related to the timely administration of thrombolytic treatment is discussed, along with the prehospital and inhospital delays that are commonly encountered. These findings have influenced major organizations such as the The Joint Commission, the American Heart Association and American Stroke Association (AHA/ASA), and the National Institute of Neurological Disorders and Stroke (NINDS), to recommend that the door to needle time of a patient experiencing ischemic stroke remain within 60 minutes. However, inhospital delays that occur during this initial golden hour for thrombolytic treatment need to be analyzed further to improve stroke care processes in the emergency department.

## **CHAPTER 3: METHODS**

### **Setting**

The study took place in a community healthcare organization in Central Florida. The organization is a primary stroke care center, certified by the Florida Agency for Health Care Administration (AHCA). A primary stroke center is a healthcare facility where medical professionals work together to provide rapid evaluation, treatment, and early rehabilitation of acute stroke patients. The AHCA criteria for stroke center certification is similar to the criteria established by the Joint Commission and is outlined in Appendix A.

### **Sample Criteria and Method of Data Collection**

A purposive sample of all patients admitted with the diagnosis of ischemic stroke and received antithrombotic treatment such as intravenous tPA, in the emergency room was included in the study. Patients who developed ischemic stroke and received thrombolytics during the course of their hospitalization were excluded from the study. Records with missing information about primary time factors, as discussed in the procedure section were excluded from the study.

The data were extracted from the patient's electronic health record and the stroke alert process time log, which is maintained on each individual patient diagnosed with ischemic stroke in the emergency room. The organization utilizes the Eclipsys® electronic health record centered on the Sunrise Clinical Manager™. The sampling period extended from January 2009 to February 2012. This time period was chosen as the stroke alert process time log was available only for this period. Data from 2008 when the healthcare facility initially became certified as a

Primary Stroke Center were unavailable and hence not included in the study. Due to the low incidence of tPA administration, data from 40 patients were obtained from this time frame.

### **Protection of Human Subjects**

Approval was obtained from the Institutional Review Boards (IRBs) of both the local community hospital organization as well as from the University of Central Florida, prior to beginning data collection. Any amendment to the protocol was requested and approved by both of these IRB's prior to data collection. Risk of disclosure of patient identity was minimal.

### **Study Design**

A retrospective descriptive design was utilized to identify areas of delay in the stroke alert process that hinder the administration of tPA within 60 minutes of patient arrival to the emergency room. This design was chosen to allow a retrospective chart review to identify areas where process improvement can be made in the treatment of ischemic stroke patients. The steps involved in the stroke alert process are outlined in Figure 1. Some of the threats to internal validity of the proposed design include incomplete documentation, problems in verification of documented information and variance in time documentation by medical professional. These threats were resolved and addressed utilizing the plan outlined in Table 5. These threats were found to be minimal as trained members of the stroke alert team maintained the running time log during the care of a patient who presented to the emergency room with ischemic stroke type symptoms.

**Table 4: Sample Stroke Alert Time Log**

---

Time	Event
.....	Time of arrival or time identified with stroke symptoms
.....	Time patient last seen normal
.....	Time stroke alert was called
.....	Time patient was first evaluated by a physician
.....	Time specimen was sent to lab
.....	Time order entered for CT scan
.....	Time CT done
.....	Time CT results called to MD
.....	Time labs results become available
.....	Time neurologist consulted via Teleneuro System
.....	Time call returned by teleneurologist and patient is evaluated
.....	Time tissue plasminogen activator initiated

---

Note. CT = computerized tomography; MD = doctor of medicine.

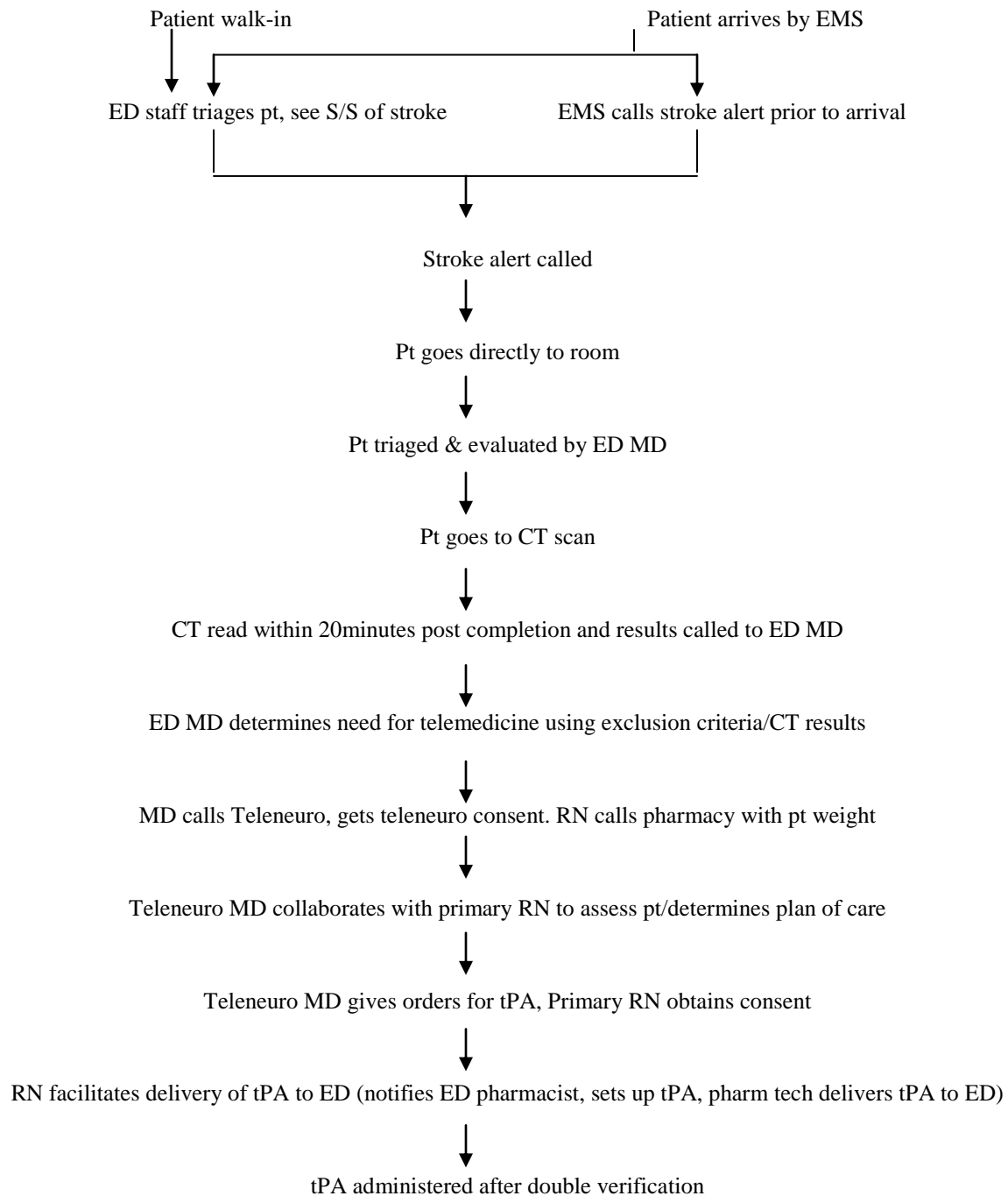


Figure X. The figure outlines the steps generally followed in the community hospital when a patient presents with a stroke. tPA = tissue plasminogen activator, MD = doctor of medicine, RN = registered nurse, ED = emergency department, CT = computerized tomography, EMS = emergency medical service, S/S = signs and symptoms.

### Figure 1: Ischemic Stroke Alert Process

## **Procedures**

A computerized database review was executed for all patients who received tPA in the emergency room during a three year period from January, 2009 to February, 2012. The sample size obtained was 40 patients. Based on record review, patients were divided into two main categories, those with door to needle time of less than 60 minutes and those with door to needle time of greater than 60 minutes. Patient characteristics such as age, gender, ethnicity, mode of arrival, presence of family, type of insurance and National Institute of Health Stroke Scale (NIHSS) score was extracted for both sets of patients. Further extensive event time analysis was done on these patients. The time factors documented in the stroke alert time process log (Table 5) were retrieved from a separate database kept in the emergency room. The lack of availability of door to time the consent was signed was considered a drawback as anecdotal information suggests that time needed to allow patient families to decide on treatment choices increases the time before medication can be given.

The initial data file included the patient medical record number and was kept on a password-protected computer. Prior to removal of medical record number, the data were coded and each patient was assigned a unique number identifier. The medical record number and the associated unique number identifiers were kept locked in a separate cabinet at the organization to maintain patient confidentiality, and was accessible only by the primary investigator. The initial data file was destroyed after coding. Each patient received the same unique number identifier for their associated stroke alert process time log data file. A random subset of 5 charts using the medical record number was retrieved for verification of the integrity of the data in the electronic database.



**Table 5: Threats to Validity**

Threats	Resolution Plan
Incomplete Documentation	Missing documentation in demographic characteristics was obtained by reviewing patient records such as face sheet, history and physical notes or consultation notes. Missing documentation in time log was retrieved by reviewing the Sunrise Clinical System. For example, if time data is missing as to when the lab results were called; this may be obtained from the computer clinical system. The real time documented as to when the lab results were entered by the laboratory personnel will be utilized in this instance. Another example would be missing time as to when thrombolytic administration was initiated. This time was retrieved from the time documented in the Medication Administration Record available in the Sunrise Clinical System.
Variance in time documentation	This was considered to be minimal as members of the stroke alert team has been trained to follow one time device in maintaining the time log such as the clock in the room, or the time available on the computer on wheels available in patient room.
Problems in verification of data collected	Five charts were randomly pulled and were reviewed for verification of data collected and time documented.

## **Statistical Analysis**

Statistical analysis was conducted using PASW® Statistics GradPack for MAC® database (version 20.0, SPSS, Chicago, IL, USA). Statistical significance was set at  $p < 0.05$ . The research questions and the associated statistical analysis utilized outlined below:

1. Do patients who have times to administration of TPA greater than 60 minutes differ significantly from patients who have times equal to or less than 60 minutes?

Descriptive statistics including mean, median, and percentages, were used to summarize patient characteristics. In addition, patient demographic characteristics and clinical characteristics were compared between patients with door to needle time of less than 60 minutes and those with needle time greater than 60 minutes. Percentages were reported for categorical variables and mean plus standard deviation will be reported for continuous variables. In order to examine and identify differences between the two groups with regard to patient characteristics, t-Test was used for continuous variables and Chi Square analysis or Fisher's Exact test was used for nominal variables.

2. What are the in-hospital factors that increase time to administration of tPA in stroke patients who patients who seek medical attention within the critical four hour window and qualify for thrombolytic treatment?

The time variables for analyses were calculated from the stroke alert process time log and included:

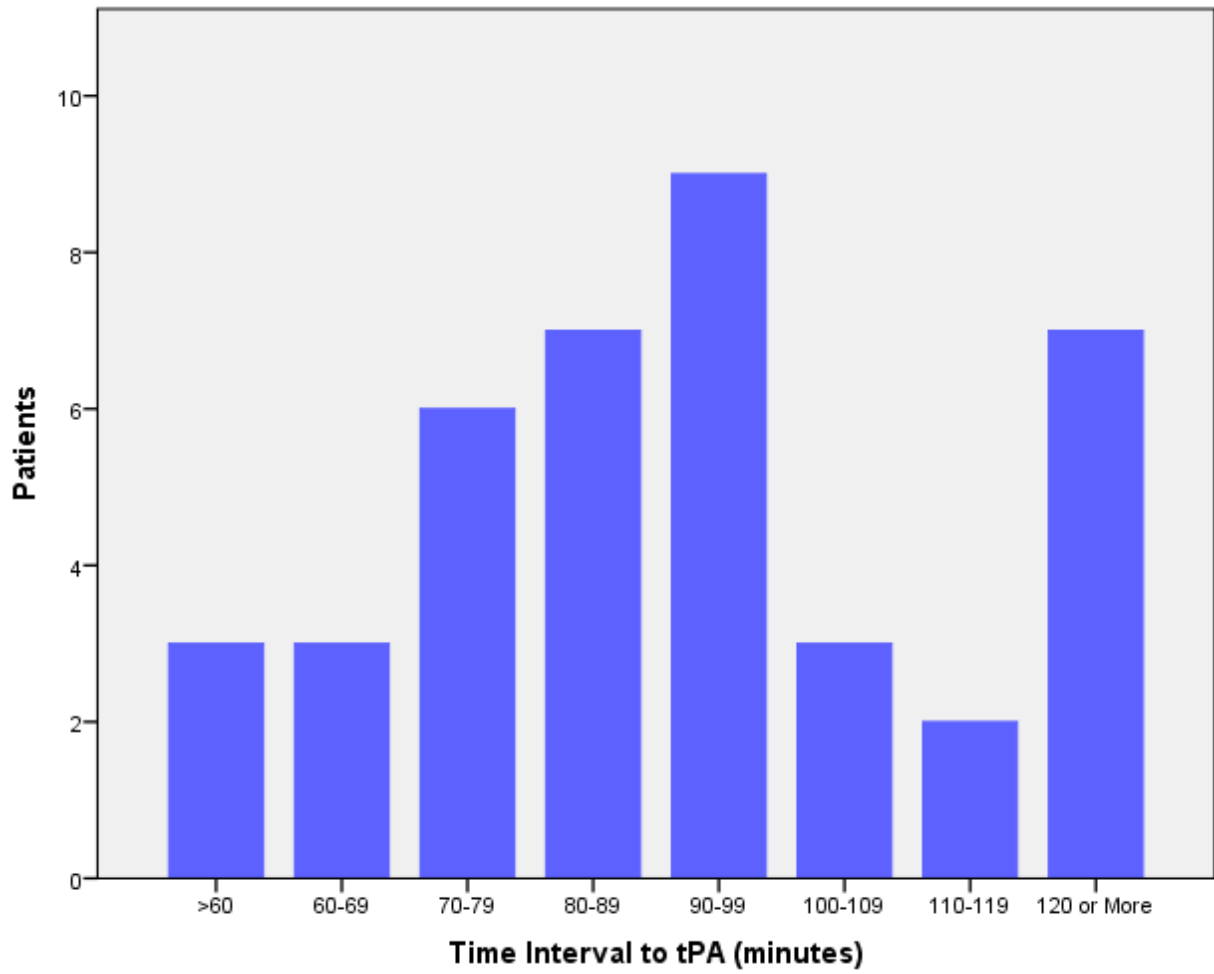
- Onset of symptoms to door time.
- Door to time stroke alert called.
- Door to first evaluation by physician.

- Door to time CT results reported.
- Door to time lab results become available.
- Door to evaluation by teleneurologist.
- Door to tPA administration time.

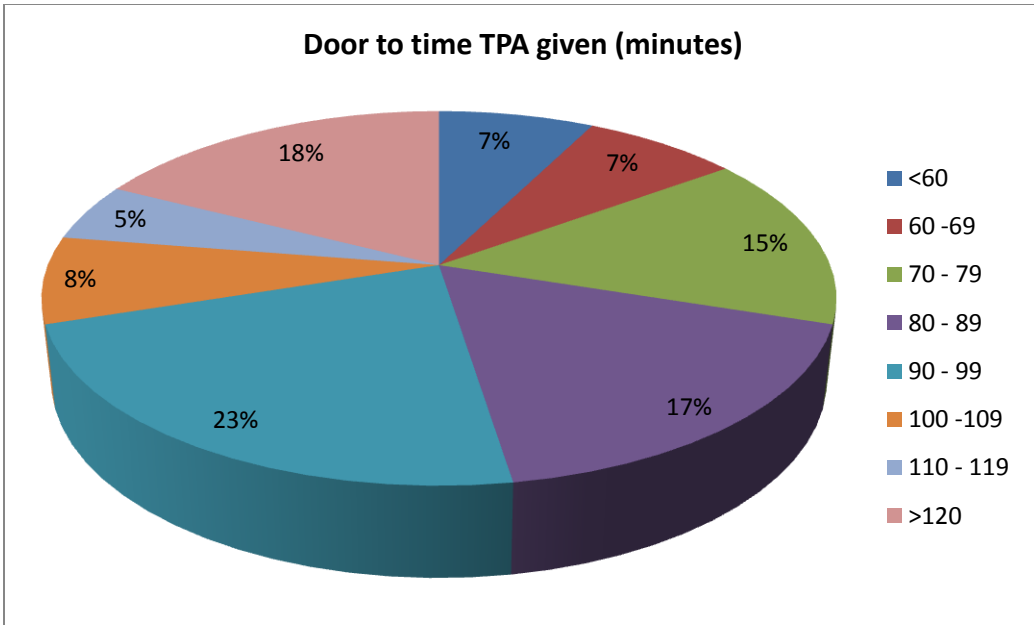
Descriptive statistics such as mean, median and standard deviation were used to summarize the time intervals and identify areas in the stroke alert care process with increased time from door to activity leading to tPA administration. Mann-Whitney U or the Student's t-test was used to identify if any differences existed in the time intervals for the two groups.

## **CHAPTER 4: RESULTS**

During the 3 year study period, a total of 40 acute ischemic stroke patients who presented to the ER and were treated with intravenous tPA were obtained. The target door to tPA time of less than 60 minutes was achieved in only one patient ( 2.5%). However, two patients received tPA within 62 minutes of arrival to the ER. Since a variety of clocks were used to determine times documented in the stroke alert log, these patients were included with the group that met the door-to-drug time goal. The small sample size of the group meeting the time goal made statistical analysis difficult. Door to tPA time exceeded 60 minutes in the remaining 37 (92.5%) patients as shown in Figure 2. Seven patients (17.5%) was 60 minutes outside the recommended time goal of 60 minutes. Approximately 70 % of the patients who received tPA, were 20 minutes out of the recommended time frame (Figure 3), thereby raising concerns of a systems problem in the care of an acute ischemic stroke patient presenting to the ER.



**Figure 2: Number of Patients and Time Interval to tPA Administration**



**Figure 3: Percentages of Door to Time tPA given for the Entire Group of Patients**

Demographic characteristics for the total sample as well as those meeting or exceeding the 60 minute goal are shown in Table 6. Both groups were similar in terms of age and gender. In the group which received tPA within 60 minutes, 33% are male and 67% are female. In the group who exceeded 60 minutes, 41% are male and 59% are female. The mean age of the group which met the time goal and those that did not meet were similar,  $64.33 \pm 13.50$  and  $64.92 \pm 16.55$  respectively.

Half the patients were Caucasian, while the remaining patients were evenly divided between Hispanics (25%) and African Americans (25%). Of those who received tPA within the 60 minute target, two were Caucasian and one was Hispanic. All 3 patients who received tPA within the goal time were insured while 16 % in the other group were uninsured. Families for all 3 patients who received tPA within the target time arrived with the patient, but they were also present in 92.5% of cases where door to drug targets were not met. Overall, there were no significant differences between the groups.

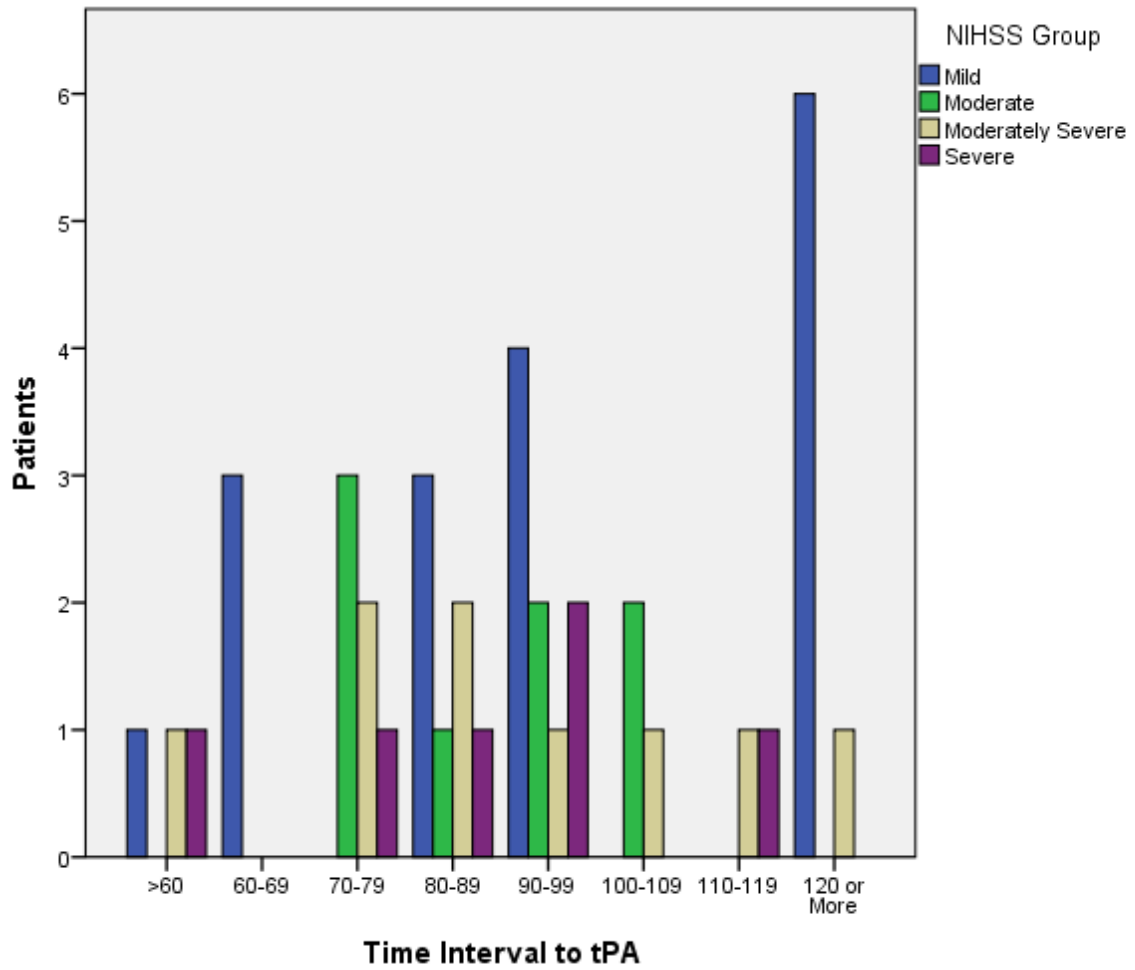
Most patients (n=32, 80%) arrived at the ER by ambulance. The mean time from onset of symptoms to arrival at the ER was just over 1 hour ( $68.03 \pm 40.04$  mins) for the entire group of patients. Although the group meeting the door to drug goal took longer to get to the ER (94 vs. 66 mins), the difference was not significant. Nearly half of all patients (42.5%) were classified as having a mild stroke while only 15% were diagnosed with a severe stroke. The median NIHSS score for the entire group was 11.50 (IQR: 4.25 to 17.75). When time interval to tPA administration was clustered against NIHSS score severity, no discernible pattern emerged for early tPA administration (Figure 4).

**Table 6: Comparison of Characteristics of Ischemic Stroke Patients with Door to tPA time of Greater than 60 Minutes and those Less than 60 Minutes**

Characteristic	Total Sample (n = 40)	≤ 60 minutes (n=3)	≥ 60 minutes (n=37)	p
	M (SD) Median	M (SD) Median	M(SD) Median	
Age	64.88 (16.20) 66.50	64.33 (13.50) 64	64.92 (16.55) 67	0.953
Onset of Symptoms to Door	68.03 (40.04) 48.50	93.67 (40.54) 96	65.95 (39.46) 48	0.254
	N (%)	N (%)	N (%)	
Gender				
Male	16 (40%)	1 (6.2%)	15 (93.8%)	1.00
Female	24 (60%)	2 (8.3%)	22 (91.7%)	
Ethnicity				
Caucasian	20 (50%)	2 (10%)	18 (90%)	0.582
African American	10 (25%)	0 (0%)	10 (100%)	
Hispanic	10 (25%)	1 (10%)	9 (90%)	
Mode of Arrival				
EMS	32 (80%)	1 (3.1%)	31 (96.9%)	.096
Walk in	8 (20%)	2 (25%)	6 (75%)	
Presence of Family				
Yes	37 (92.5%)	3(100%)	34 (91.9%)	1.00
No	3 (7.5%)	0	3 (100%)	
Type of Insurance				
Medicare	17 (42.5%)	1 (5.9%)	16 (15%)	0.61
Private	17 (42.5%)	2 (11.8%)	15 (88.2%)	
Uninsured	6 (15%)	0	6 (100%)	
	Median (IQR) N (%)	N (%)	N (%)	
Stroke Severity (NIHSS Score)	11.50 (4.25, 17.75)			0.657
Mild	17 (42.5%)	1 (33.3%)	16 (43.2%)	
Moderate	8 (20%)	0 (0%)	8 (21.6%)	
Moderately Severe	9 (22.5%)	1 (33.3%)	8 (21.6%)	
Severe	6 (15%)	1 (33.3%)	5 (13.5%)	

Note: EMS = emergency medical personnel, NIHSS = National Institute of Health Stroke Scale





**Figure 4: Comparison of Time to tPA Administration against severity of NIHSS score**

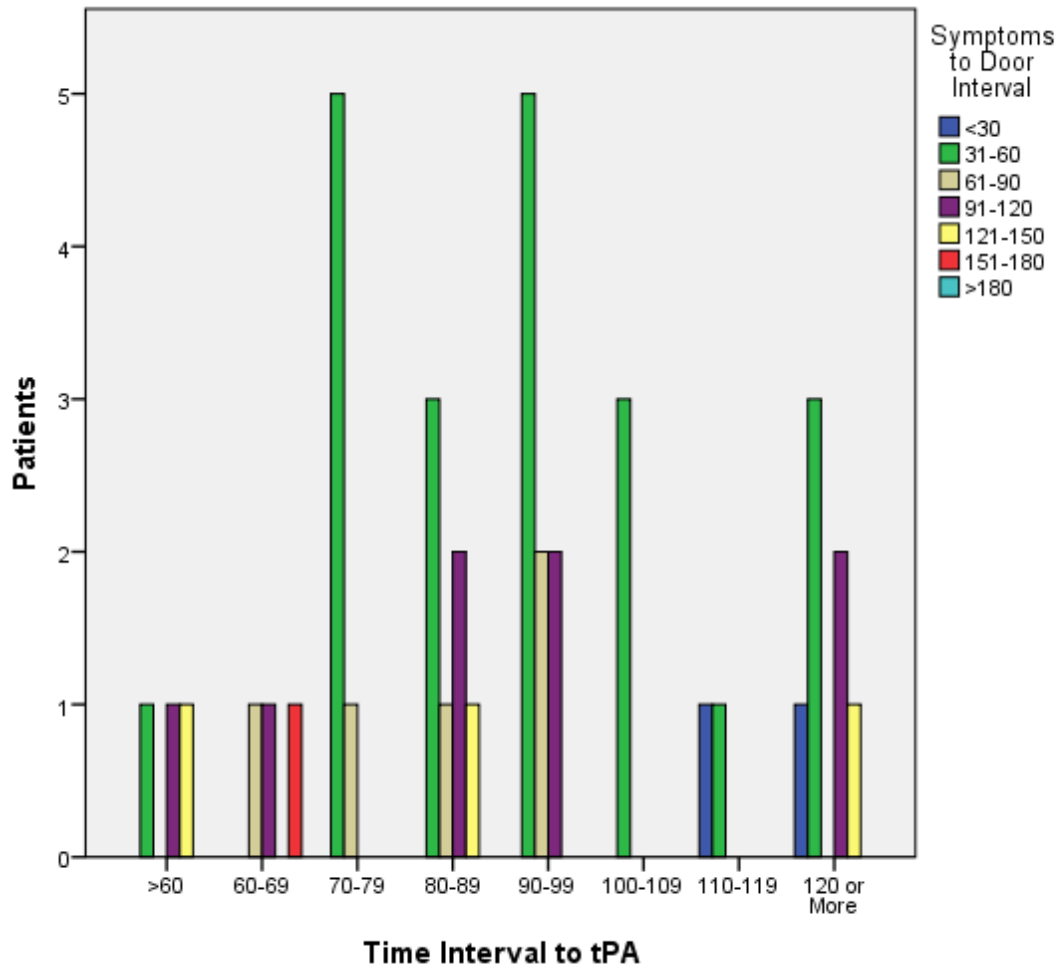
Time intervals associated with the acute stroke alert care process are shown in Table 7. Overall, mean door to tPA time of 96 minutes was 36 minutes longer than the recommended door to tPA target time. There may be a lack of urgency when patients presents early on from the initial onset of their stroke symptoms. Patients who presented within 30 minutes of onset of stroke symptoms had a door to tPA time of greater than 100 minutes (Figure 5). However, no discernible pattern was observed when clustering onset of symptoms to door and time to tPA administration.

There were no significant differences for any time intervals between door to tPA groups. The standards for time intervals set by the AHA/ASA and the Joint Commission is 45 minutes for lab results from the time it was ordered and 45 minutes for the time CT was obtained and interpreted. This was achieved in 87.5% of the patients ,both for lab results as well as for CT results. The standard time goal for physician evaluation of an ischemic stroke patient's arrival is 10 minutes and this was achieved in 80% of the patients. The mean time interval associated with door to teleneurologist evaluation was close to an hour ( $52.65 \pm 19.86$  mins) with a median of 39 minutes. However, no standard time frame has been set for this time interval.

During this retrospective chart review some of the identifiable delays included patients with patients with difficult intravenous accesses, patients with unstable hemodynamic, respiratory failure requiring intubation, and patients with unusual history or presentation.

**Table 7: Time Intervals Associated with the Acute Stroke Alert Care Process**

<b>Interval</b>	<b>Total (n=40)</b>	<b>≤ 60 minutes (n=3)</b>	<b>≥ 60 minutes (n=37)</b>		
	<b>M (SD) Median</b>	<b>M (SD) Median</b>	<b>M (SD) Median</b>	<b>Differences in Mean (95% CI)</b>	<b>P</b>
Door to Stroke Alert Called	9.80 (13.38) 4.00	3.33 (0.58) 3.00	10.32 (13.80) 4.00	-6.99 (-23.30 to 9.32)	0.63
Door to MD Evaluation	7.75 (8.86) 5.00	8.00 (1.73) 9.00	7.73 (9.21) 4.00	0.27 (-10.63 to 11.20)	0.21
Door to CT Results	29.93 (12.69) 25.50	19.67 (3.06) 19.00	30.76 (12.83) 27.00	-11.10 (-26.29 to 4.11)	0.08
Door to Lab Results	24.08 (22.06) 19.00	30.0 (1) 30.00	24.38 (22.5) 19.00	5.62 (-21.47 to 32.71)	0.43
Door to Teleneurologist Evaluation	52.65 (19.86) 50.00	35.33 (6.35) 39.00	54.05 (19.95) 51.00	-18.72 (-42.39 to 4.95)	0.72
Door to Time TPA given	96.13 (28.06) 90.00	59.67 (4.04) 62.00	99.1 (27.10) 93.00	-39.41 (-71.44 to - 7.39)	0.00



**Figure 5: Comparison of Onset of Symptoms to Door and Door to tPA Administration Time Interval**

## CHAPTER 5: DISCUSSIONS

Despite various organizational recommendations, guidelines and multiple studies showing the benefits of early reperfusion therapy in acute ischemic stroke patients, meeting the goal of administration of tPA within 60 minutes of patients arrival to the ER remains elusive. This study revealed that only 7.5% of the patients who presented to the ER received tPA within the recommended time frame of 60 minutes. Though this number is alarming, it remains consistent with other nationwide studies reporting low % of compliance with door to tPA times and calls for an aggressive quality improvement initiative in the care of an acute ischemic stroke patient. In approximately 25, 000 patients that presented to US hospitals participating in Get With the Guidelines-Stroke (GWTG-Stroke), only one third received tPA within the recommended 60 minutes of arrival to the ER. The median door to tPA time in this entire group was found to be 78 minutes (Fonarow, Smith, Saver, et al., 2011). Another national study involving 57 academic and community centers reported a median door to tPA time of 96 minutes accounting for less than one third of the total patients who received tPA in their study period (Albers, Bates, Clark et al., 2000). However, an international study conducted in a community hospital reported a mean door to tPA time of 38 minutes, after the implementation of major organizational and structural changes in the ER (Tveiten, Mygland, Ljøstad, & Thomassen, 2009).

Another interesting observation from this study was that patients with shorter onset of symptoms to door had longer door to tPA time. The median onset of stroke symptoms to door time between the group that received timely tPA and those that received delayed tPA was 96 and 48 minutes respectively. This finding of delayed treatment is consistent with other studies where

"having more time" translated into "taking more time" for tPA administration (Fonarow, Smith, Saver, et al., 2011, Ferrari, Knoflach, Kiechl, et al., 2010). The door to tPA time was found to be much higher in patients that arrived within 60 minutes from onset of their stroke symptoms when compared to patients who arrived 61 to 120 minutes and 121 to 180 minutes (Ferrari, Knoflach, Kiechl, et al., 2010). This may be attributed to the lower sense of perceived urgency and the feeling of still having enough time to administer tPA within the 4 hour window, thereby causing varying degrees of small delays in the different steps involved in the stroke alert care process.

***Time from door to stroke alert called:*** This is a critical element of the multidisciplinary stroke care process, as timely recognition of stroke by following acute triage protocols reduces time to tPA and enhances stroke care. When a patient is suspected to have stroke type symptoms in the ER, the triage nurse alerts the ER physician. If the ER physician concurs with the assessment, the request for a stroke alert is made. The ER contacts the main hospital operator who then sends out a central page, alerting the stroke team. If the patient is arriving by EMS and the ER is notified that it is a stroke code, then a central page is also sent out including the estimated time of arrival. Once the stroke alert is called, the multidisciplinary team convenes at the patient bedside. The median door to time stroke alert was called was 4 minutes. Proper prioritization should be given to the stroke patient in the context of the overall activity of the busy emergency room. Strokes should be considered a time-sensitive condition and rapid diagnosis and treatment are essential. Activating the stroke team is the first step in achieving this goal. (Gomez, Malkoff, Sauer, et al., 1994).

***Time from door to MD evaluation:*** In this study, the median door to MD evaluation time was 5 minutes for the entire group of 40 patients. The mean was also below the 10 minute target.

This was within the target time of 10 minutes for door to MD evaluation as recommended by the National Institute of Neurological Disorders and Stroke (NINDS) and the Joint Commission (JC). This phase of the process will not be a target for quality improvement.

***Time from door to CT results:*** The JC recommends that a CT scan be ordered within 25 minutes of patients arrival to the ER, with results interpreted within 45 minutes. Though the exact time of CT order entry was not analyzed for this study, the mean door to interpreted CT results was  $19.67 \pm 3.06$  minutes for the group who received tPA within 60 minutes and  $30.76 \pm 12.83$  minutes for those who received tPA after 60 minutes. This target was easily achievable due to the presence of the CT scanner within the department that is primarily used for the ER patients only. However, there is room in this time interval for improvement, with close proximity and accessibility to a CT scanner. The rebuilding of an ER with a CT scanner as well as with prenotification by EMS enabled one hospital to drop its CT delay time from  $63 \pm 14$  minutes to  $7 \pm 2$  minutes (Lindsberg, Häppölä, Kallela, et al., 2006). They were further able to reduce their door to tPA time from  $88 \pm 7$  minutes to  $50 \pm 3$  minutes ( $p < 0.0001$ ).

***Time from door to lab results:*** This time interval was again within the target goal set by the national agencies where lab results are to be completed and reported within 45 minutes. The mean time interval for door to lab results was  $24.08 \pm 22.06$  for the entire group.

***Time from door to teleneurologist evaluation:*** The mean time interval associated with door to teleneurologist evaluation was  $52.65 \pm 19.86$  minutes with a median of 51 minutes for those who received tPA after 60 minutes of their arrival to ER. Though no specific time goal has been set by national organization for door to evaluation by teleneurologist, the study did show that this time interval warrants improvement by addressing potential sources of delay. More

specific documentation of time such as the time teleneurologist was called, time of call back, time of initial evaluation, time orders for tPA administration were given would enable closer tracking of the process.. Additional documentation of potential delays such as delay in set up, lack of remote technical connectivity, and language barriers needs to be noted. Previous studies have demonstrated a delay in neurologic consultation, but were not specific to teleneurologist evaluation. A median delay of 180 minutes (Morris, Rosamond, Madden et al., 2000) and 21.28 minutes (Keskin, Kalemoglu & Ulusoy, 2005) was found for obtaining neurospecialist consultation. A recent retrospective study compared face to face evaluation (n=52) with teleneurologist evaluation (n=45) in the delivery of tPA in a single hospital (Chowdhury, Birns, Rudd, & Bhalla, 2012). The time intervals associated with door to CT, CT to drug and door to drug were significantly better in the face to face evaluation group. Additional time may have been utilized in obtaining consent for telemedicine evaluation and completion of telemedicine consultation and assessment as well as related to technology failures (Chowdhury, Birns, Rudd, & Bhalla, 2012).

### **Recommendations**

Multiple studies have shown the efficacy and long term benefits of early thrombolytic administration in acute ischemic stroke patients. However, in spite of guidelines and recommendations made by various national and international agencies, obstacles remain in the translation of research into effective clinical practice. Analysis from this study yielded results consistent with previous studies in regards to the alarmingly low rate of administration of tPA within 60 minutes of an eligible stroke patient's arrival to the ER. The delivery of tPA with a short door to needle time calls for complex clinical process that requires coordination between



departments and disciplines for timely triage, diagnosis, decision making and treatment of an acute ischemic stroke patient. A multidimensional, highly coordinated focused effort is necessary to bring about successful organizational change in this complex process (Schwamm, Pancioli, Acker, Goldstein, et al., 2005).

## **Organizational Strategies**

Lessons pertaining to organizational structure can be learned and applied from hospitals that succeeded in reducing their door to balloon time in the care of their patients presenting with acute ST-elevation myocardial infarction. Door to balloon time can be similar to door to tPA time in that, both involves a complex clinical process requiring interdepartmental and interdisciplinary coordination. The key organizational culture and structural strategies of these successful hospitals was analyzed in a qualitative study that included 11 hospitals (Bradley, Curry, Webster, Mattera, et al., 2005). These strategies applied to stroke care are as follows:

- The presence of a shared organizational explicit goal of reducing the door to drug time to less than 60 minutes.
- The presence of visible senior management that show an interest in door to drug time as it is an indicator of overall hospital performance.
- The presence of uncompromising clinical leaders such as nurses, advanced practice nurses and physicians who are committed in their efforts to achieve the goal of improving door to drug time.
- The presence of organizational culture that fosters persistence despite challenges and setbacks and avoids finger pointing, taking a non blaming approach.

- The presence of continual data feedback to monitor progress and identify problems and successes.
- The establishment of a collaborative interdisciplinary team.
- The availability and development of standardized stroke care protocols and flexibility in implementing these protocols based on rapid cycle feedbacks. Unsuccessful strategies are dropped in the process, and successful strategies implemented.

## **Practice Strategies**

A national quality improvement initiative, *Target:Stroke*, was developed by the American Heart Association/American Stroke Association (AHA/ASA) with the goal to improve stroke care by focusing on reducing door to thrombolytics time in acute ischemic stroke patients and to increase the number of eligible stroke patients that receive thrombolytics within 60 minutes of arrival to the hospital (Fonarow, Smith, Saver, Reeves, et al., 2011b). Based on the key best practice strategies recommended by the Target:Stroke initiative, the following areas will have to be revisited and re-evaluated to shorten the door to tPA time:

- Advance hospital notification by EMS: Advance notification can prepare ER personnel for the arrival of the patients and ensure that the CT Scanner, when appropriate, will be freed up for the arrival and use of the stroke patient.
- Single call activation system: This system is already in effect at the community hospital where a single call from the ER to the central page operator activates the "Stroke Code" and notifies the stroke team of the patient's arrival.

- Rapid triage protocol and stroke team notification: Timely recognition of stroke by utilization of acute triage protocol being in place.
- Stroke tools: Once a stroke alert is called, a pre-prepared stroke packet is used consisting of NIHSS scale, guidelines, stroke specific order sets, clinical decision support, hospital specific algorithms of stroke pathway, and stroke alert time log is accessed for each patient.
- Rapid acquisition and interpretation of brain imaging: The availability of CT scanner within the ER in this community hospital and the immediate notification of the radiologist should not cause any delay in this step of the stroke care process.
- Rapid laboratory testing: The availability of the pneumatic tube system for blood transport to the lab and the availability of a laboratory technician on the stroke team has ensured that the target goal of lab results being available within 45minutes .
- Mix tPA medication ahead of time: The AHA/ASA best practice strategy calls for mixing the drug, setting up the bolus dose and one hour on the infusion pump, once a patient is recognized as a potential tPA candidate. This would shorten the time to treatment once a decision has been made and consent is signed. However, the hospital pharmacy needs to ensure that no financial risk is involved and further look into pharmaceutical company policies where drugs may be replaced free of charge if not used during time critical emergency situations (Fonarow, Smith, Saver, Reeves, et al., 2011).

- **Rapid access to intravenous tPA:** The current stroke care system receives its drug from the central pharmacy once the decision to infuse tPA has been made. Changes to pharmacy protocol need to be considered where tPA will be stored in the ER and can be accessed by the ER pharmacist during a stroke code. Standardized order sets and dosing charts can be made available in the computer Sunrise system to prevent dosing errors and facilitate timely administration of tPA.
- **Team based approach:** The interdisciplinary collaborative team needs to meet on a monthly basis to discuss care quality, stroke performance improvement efforts, patient safety and clinical outcomes. Recommendation for improvement and monitoring can be made. Based on this study, the stroke alert time log can be revised (Table 9), to include other key time factors such as time order for tPA given, and time consent was signed. In order to ensure correct documentation of time, an atomic time clock can be placed in all acute ER rooms as well at the initial triage area. Staff need to be educated that only these clocks can be used for time documentation.
- **Prompt data feedback:** A data monitoring and feedback system needs to be established where timely feedback can be provided on a patient by patient basis. This will help the stroke team identify specific delays, set targets, and take appropriate actions.

Furthermore, in-services and education of ER and other pertinent staff need to be conducted so they perceive a stroke alert with the same sense of urgency as assigned to a cardiac

alert or trauma alert. They need to realize that with each passing minute and activity, the brain is dying and irrevocable damage is being done to millions of brain cells. It is also important to acknowledge the fact that door to drug time of less than 60 minutes may not be achievable in all patients presenting with acute ischemic stroke symptoms. Quality, safety and outcome data needs to be regularly and closely monitored for any possible unintended consequences from rushed assessments, dosing errors or complications. Taking into consideration these unavoidable circumstances, the JC's target is to achieve a door to tPA time of less than 60 minutes in at least  $\geq 80\%$  of the patients presenting to a primary stroke center. Thrombolytics can be administered in a safe and effective manner and timely administration can be a reality for majority of the patients (Schwamm, Pancioli, Acker, Goldstein, et al., 2005).

**Table 8: Revised Stroke Alert Time Log**

---

Time	Event
.....	Time of arrival or time identified with stroke symptoms
.....	Time patient last seen normal
.....	Time stroke alert was called
.....	Time patient was first evaluated by a physician
.....	Time specimen was sent to lab
.....	Time order entered for CT scan
.....	Time CT done
.....	Time CT results called to physician
.....	Time labs results become available
.....	Time Tele-neuro System set up in patient room
.....	Time neurologist consulted
.....	Time call returned by teleneurologist
.....	Time evaluation performed by teleneurologist
.....	Time order for tPA given
.....	Time consent for tPA signed
.....	Time tPA arrived from pharmacy
.....	Time tissue plasminogen activator initiated

---

Note. CT = computerized tomography.

### **Limitations**

The study posed several challenges. First, the lack of adequate record keeping and loss of records during the initial period of certification as a primary stroke center limited a complete analysis of all patients who received tPA in the selected time frame. Second, the sample size was small and limited extensive statistical analysis. Third, it would have been valuable to study other key time factors such as time the drug was ordered and time the consent was signed, however, these were not captured in the stroke log or medical record. Nevertheless, this study will serve as a stepping stone to implement further quality initiatives and strategies in the care of a patient presenting with acute ischemic stroke.

### **Future Research**

The present study provides an opportunity for continued evaluation of quality improvement and performance measures to ensure that acute ischemic stroke patients are treated in a timely manner. Detailed data feedback, a patient focused organizational culture and interdisciplinary team work will facilitate accountability and help achieve improvement in door to tPA times. In addition to ongoing assessment and evaluation, time series analysis can also be conducted to identify areas of potential delays. Other potential influences such as provider specific delays, time of the week, time of the day can also be analyzed.

### **Summary**

The therapeutic benefits of intravenous tPA is time dependent in an acute ischemic stroke patient and is an important determinant of 90 day and one year functional outcomes. For every 15minute reduction to the start of reperfusion therapy, there is 5% lower odds of risk adjusted in-hospital mortality. For every 10 minute delay to the start of reperfusion therapy, 20 million nerve cells die and one fewer patient of 100 patients have improved functional outcomes. This has

resulted in national organizations setting a target door to drug time of less than 60 minutes in acute ischemic stroke patients. The study revealed that only 7.5 % eligible tPA patients received the drug within 60 minutes of arrival, with shorter onset of symptoms to arrival time having longer door to tPA time. These findings support the need to re-evaluate the stroke care process in the ER, without compromising short term clinical outcomes. Organizational strategies and clinical practice strategies discussed will have to be implemented to improve timely tPA administration, thereby integrating evidence into clinical practice in the care of an acute ischemic stroke patient.



**APPENDIX A: CRITERIA FOR PRIMARY STROKE CENTER  
CERTIFICATION**

# Updated Primary Stroke Center Certification Appendix for the Disease-Specific Care Manual

This article provides a revised Primary Stroke Center Certification appendix for the *Disease-Specific Care Certification Manual, Second Edition*. It updates standard references appearing in the "Brain Attack Coalition Recommendation/Joint Commission Expectation" cross-walk. The entire appendix is presented for your conven-

ience. New language is indicated with underline and deleted text is indicated with strikethrough. For questions about disease-specific care certification and this appendix please visit the Joint Commission's Web site at <http://www.jcaho.org> or call 630/792-5291. ▲



## OFFICIAL PUBLICATION OF UPDATED APPENDIX

### Appendix: Primary Stroke Center Certification

#### APPLICABLE TO DISEASE-SPECIFIC CARE

Effective July 1, 2005

[Revision: Updated standards references in Stroke Addendum to refer to current standard numbers.]

#### APPENDIX: PRIMARY STROKE CENTER CERTIFICATION

##### Primary Stroke Center Certification Program

The Joint Commission's Primary Stroke Center Certification Program is based on the Recommendations for Primary Stroke Centers published by the Brain Attack Coalition and American Stroke Association statements for stroke to evaluate hospitals functioning as Primary Stroke Centers.

The on-site review team will include a health care professional with experience in treating stroke and implementing Primary Stroke Centers.

##### Eligibility

In addition to the eligibility requirements outlined in the *Disease-Specific Care Certification Manual*, programs seeking Primary Stroke Center Certification must use a standardized method of delivering clinical care based on the Brain Attack Coalition's Recommendations for Primary Stroke Centers and guidelines developed by the American Heart Association/American Stroke Association (AHA/ASA) or equivalent evidence-based guidelines. Please refer to the AHA/ASA Web site for additional information (<http://www.americanheart.org/presenter.jhtml?identifier=3004586>).

##### Requirements

- Standards.** Hospital programs applying for Primary Stroke Center Certification will be evaluated using the standards listed in the *Disease-Specific Care Certification Manual*.
- Clinical Practice Guidelines.** The methods for evaluating compliance will include evaluating conformity with the Recommendations for Primary Stroke Centers, developed by the Brain Attack Coalition and published in the *Journal of the American Medical Association* (see pages 4–6 for additional information). In addition, hospitals will be expected to demonstrate their application of and compliance with the guidelines published by the AHA/ASA relevant to the stroke patient being treated.

- Performance Measures.** The ASA and the Joint Commission in addition to a jointly sponsored stroke advisory panel have reached consensus on a standardized set of performance measures for stroke. Disease-specific care (DSC) programs seeking certification are required to collect data on the first four measures of the standardized measure set (see below). Performance measure details are provided in the DSC Certification Program Performance Measurement Implementation Guide for Stroke.

Standardized Performance Measures for Stroke	
Set – Measure	Disease-Specific Care Performance Measure Name
Stroke-1*	DVT Prophylaxis
Stroke-2*	Discharged on Antithrombotics
Stroke-3*	Patients with Atrial Fibrillation Receiving Anticoagulation Therapy
Stroke-4*	Tissue Plasminogen Activator (t-PA) Considered
Stroke-5	Antithrombotic Medication Within 48 Hours of Hospitalization
Stroke-6	Lipid Profile
Stroke-7	Screen for Dysphagia
Stroke-8	Stroke Education
Stroke-9	Smoking Cessation
Stroke-10	A Plan for Rehabilitation Was Considered
* Required measures	
<b>Note:</b> All 10 measures comprise a set for pilot testing.	

(Continued on page 4)

## Updated Primary Stroke Center Appendix (continued)

(Continued from page 3)

Appendix: Primary Stroke Center Certification (Continued)		
Primary Stroke Center Certification		
Major Element	Brain Attack Coalition Recommendation	Joint Commission Expectation
<p><b>1. Hospital and Administrative Support</b></p>	<p>Organizational support and commitment from executive level administration shows designation of a stroke medical director and medical staffing by physicians with expertise in cerebrovascular disease.</p> <p>Written documentation from administration outlines the designation and authority of acute stroke teams.</p>	<p>Written documentation shows support of the Primary Stroke Center by hospital/health system administration. <a href="#">PR.2, EP.2</a> <a href="#">PR.1, EP.2</a></p> <p>A Primary Stroke Center medical director is appointed.<sup>1</sup> <a href="#">PR.2, EP.1</a> <a href="#">PR.1, EP.1</a></p> <p>Physicians on the acute stroke team have knowledge and expertise in the diagnosis and treatment of cerebrovascular disease. <a href="#">PR.4, EP.1</a> <a href="#">PR.3, EP.1</a></p>
<p><b>2. Acute Stroke Team</b></p>	<p>Written documentation indicates the following:</p> <ul style="list-style-type: none"> <li>• Stroke team composition</li> <li>• Staffing level and requirements</li> <li>• Stroke team notification system and response expectations</li> </ul> <p>Stroke team logs document the following:</p> <ul style="list-style-type: none"> <li>• Response times</li> <li>• Patient diagnosis</li> <li>• Treatments and action</li> <li>• Outcomes</li> </ul>	<p>Written documentation regarding stroke program operations delineates specific requirements and assignment of stroke team duties. <a href="#">DF.1, EP.2</a></p> <p>Written documentation exists for stroke team notification system and expected response times.<sup>2</sup> <a href="#">PR.4, EP.5</a> <a href="#">PR.3, EP.5</a></p> <p>Evidence of stroke team log that captures stroke team response time to acute stroke patients, treatment used, and patient disposition. The log can be captured by written or electronic means and/or may be done retrospectively through chart audits. <a href="#">CT.4, EP.3</a></p>
<p><b>3. Written Care Protocols</b></p>	<p>Written protocols include emergency care of patients with ischemic and hemorrhagic stroke, including stabilization of vital functions, initial diagnostic tests, and use of medication, including but not limited to r-PA treatment.</p>	<p>Protocols/care paths for the acute work-up of ischemic/hemorrhagic stroke patients are available in the emergency department (ED), acute care areas, and stroke unit (preprinted documents or electronically). <a href="#">PR.11, EP.1</a> <a href="#">PR.10, EP.1</a></p> <p>Use of the protocol is reflected in the order sets, pathways, or medical records. <a href="#">DF.2, EP.4, EP.5</a></p> <p>Protocols demonstrate that the stroke center can provide FDA-approved treatments for stroke in accordance with indications and package inserts. (For example, for institutions that deliver thrombolytic therapy, r-PA protocol is available, with a three-hour window.)</p> <p>Protocol is de novo or adapted from extant resources and published guidelines. <a href="#">DF.2, EP.1, EP.2</a></p> <p>Time parameters for stroke work-up are included in the protocol or the ED work-up protocol. <a href="#">DF.2, EP.5</a> <a href="#">EP.4</a>; <a href="#">DF.3, EP.2</a></p> <p>For Primary Stroke Centers that treat and transfer acute stroke patients, written documentation includes time parameters and transfer procedures. <a href="#">DF.2, EP.2</a></p> <p>Acute stroke protocols or order sets and pathways are included in the institution's routine process for review and updating. <a href="#">DF.2, EP.6</a>; <a href="#">DF.5, EP.2</a></p>

## Appendix: Primary Stroke Center Certification (Continued)

Primary Stroke Center Certification		
Major Element	Brain Attack Coalition Recommendation	Joint Commission Expectation
<b>4. Emergency Medical Systems</b>	EMS/ED is integrated in the care and transport of stroke patients.	A description of the EMS is complete with any available treatment guidelines for pre-hospital personnel. Also, if available, include EMS stroke patient routing plans that address transferring stroke patients to stroke centers and stroke educational initiatives of the hospital for pre-hospital personnel. If these items are not available, a plan should be provided that demonstrates an initiative by the hospital to provide such with the EMS. <u>PR.7, EP 1, EP 2, EP 3</u> <u>PR.6, EP 1, EP 2, EP 3</u>
<b>5. Emergency Department</b>	ED care providers are familiar with the care of acute stroke patients, understand how to activate the stroke team, and use care pathways/protocols for acute stroke treatment.	ED care providers show familiarity with the following: <ul style="list-style-type: none"> <li>• The pathology, presentation, assessment, diagnostics, and treatment of patients with acute stroke</li> <li>• The location and application of stroke-related protocols, activation of the acute stroke team, and communications with inbound EMS</li> <li>• The recognition, assessment, and management of acute stroke complications <u>DF.1, EP 2, EP 1, EP 5</u></li> </ul> Eighty percent of ED care providers can provide evidence of review of the institution's acute stroke protocol. The institution may choose how it will represent this evidence to the Joint Commission. <u>PR.4, EP 5</u> <u>PR.3, EP 5</u> ; <u>DF.1, EP 6</u> ; <u>DF.2, EP 9</u>
<b>6. Stroke Units</b>	Stroke units have the following: <ul style="list-style-type: none"> <li>• Trained staff</li> <li>• Appropriate monitoring</li> <li>• Stroke protocols (captured under "Written Care Protocols" section earlier in table)</li> </ul>	<b>Note:</b> <i>Stroke units can be defined and implemented in a variety of ways. The stroke unit does not have to be a specific enclosed area with beds designated only for acute stroke patients, but it will be a specified unit to which most stroke patients are admitted.</i> Care providers working in the stroke unit demonstrate evidence of initial and ongoing training in the care of acute stroke patients. They receive at least eight hours annually of continuing education or other equivalent educational activity, as determined appropriate by the stroke center director and as appropriate to the care providers' level of responsibility. <u>DF.1, EP 5, EP 7</u> Monitoring systems (as ordered) provide continuous data on the following physiologic parameters: <ul style="list-style-type: none"> <li>• Heart rate/rhythm with automatic arrhythmia detection</li> <li>• Blood pressure with noninvasive blood pressure (BP) monitoring</li> <li>• Oximetry <u>DF.2, EP 4, EP 6</u></li> </ul>
<b>7. Neurosurgical Services</b>	Neurosurgical services are available within two hours of when it is deemed clinically necessary. If the hospital is providing neurosurgical care, operating room (OR) facilities are available in that facility.	Written documentation shows evidence of neurosurgical coverage or protocol for transfer to appropriate facility. <u>PR.4, EP 1</u> <u>PR.3, EP 1</u> ; <u>PR.5, EP 1</u>  <i>For sites that do not transfer patients for neurosurgical emergencies, the stroke center has a fully functional OR facility and staff for neurosurgical services within two hours of the recognized need for such services.</i> <u>PR.4, EP 1</u> <u>PR.3, EP 1</u>
<b>8. Neuroimaging</b>	Obtain a diagnostic brain image <sup>3</sup> within 25 minutes of it being ordered, 24/7. Diagnostic image evaluated by qualified personnel within 20 minutes of completion, 24/7.	Documentation indicates that on a 24/7 basis, 80% of acute stroke patients have a diagnostic brain image (head CT) completed (and results reported to or reviewed by a member of the stroke team) within 45 minutes of it being ordered, when clinically indicated (in acute hemorrhagic or ischemic stroke resuscitation candidates). <u>PR.4, EP 1</u> <u>PR.3, EP 1</u> ; <u>PR.5, EP 1</u>

(Continued on page 6)

## Updated Primary Stroke Center Appendix (continued)

(Continued from page 5)

### Appendix: Primary Stroke Center Certification (Continued)

Primary Stroke Center Certification		
Major Element	Brain Attack Coalition Recommendation	Joint Commission Expectation
<b>9. Laboratory Services</b>	Laboratory services are available for initial stroke labs, 24/7.  Laboratory service turnaround is less than 45 minutes.  ECG and chest x-ray (as needed) are provided within 45 minutes.	Documentation indicates the ability to complete initial lab tests <sup>4</sup> and availability on site 24/7. <del>PR.4, EP.4</del> PR.3, EP.1; PR.5, EP.1  Documentation indicates the ability to complete and report lab tests in less than 45 minutes from being ordered. <del>PR.4, EP.4</del> PR.3, EP.1  Documentation indicates the ability to perform an ECG and chest x-ray within the same time frame as laboratory testing. <del>PR.4, EP.4</del> PR.3, EP.1
<b>10. Outcomes/Quality Improvement</b>	Stroke units have a method for tracking stroke performance.  Quality improvement department and stroke team collaborate in on-going quality improvement efforts in stroke care.	Evidence of specific stroke performance measurement and review by quality improvement department and stroke team exists. PM.1, EP.1; PM.2, <del>EP.3</del> EP.4, EP.5  Documentation exists to reflect the following: <ul style="list-style-type: none"> <li>• Performance measures and indicators tracked <del>PR.1, EP.2</del> PM.1, EP.2</li> <li>• Specific interventions to improve in the selected measure <del>PR.1, EP.3</del> PM.1, EP.3</li> <li>• Specific outcomes to determine success <del>PR.1, EP.3</del> PM.1, EP.3</li> <li>• Implementation period and re-evaluation point <del>PR.1, EP.3</del> PM.1, EP.3</li> </ul>
<b>11. Educational Programs</b>	Stroke centers offer at least one public education event per year.	Documentation shows at least one stroke public education activity per year. SE.3, EP.5
<p><b>Notes:</b></p> <ol style="list-style-type: none"> <li>1. A stroke center medical director does not have to be a board certified neurologist; however, that would be the optimum condition.</li> <li>2. Optimally, a care provider experienced in the diagnosis and treatment of stroke will be available within 15 minutes by telephone and at the bedside (as per a referring physician's request) of an acute stroke patient within the time period designated in the protocol and/or as instructed by the stroke center director. Response time adherence may also be accomplished through telemedicine and/or with a resident or other care provider in contact with an experienced stroke care provider within the time designated by the protocol.</li> <li>3. The brain image can be obtained by CT or MRI and needs to definitively rule out/detect intra-cranial hemorrhage, or other causes of the stroke syndrome. The imaging needs to be available on site 24 hours a day/365 days a year (barring short term-failure, whereby the hospital should divert potential acute stroke patients). However, review of the images does not have to be done on site. Evaluation can be performed off site by telemedicine technology.</li> <li>4. Lab tests include a complete blood cell count with platelet count, coagulation studies, (PT INR), and blood chemistries. DF.2, EP.4</li> </ol>		

**APPENDIX B: HEALTHCARE FACILITY INSTITUTIONAL REVIEW  
BOARD LETTER OF APPROVAL**



1414 Kuhl Ave.  
Orlando, FL 32806  
321.843.7000

orlandohealth.com

ORIGINAL

April 27, 2012

Elizabeth Joseph  
593 Highbrooke Blvd.  
Ocoee, FL 34761

Dear Ms. Joseph:

Concerning the following Study:

**Our Study #** 1205104      **At:** Orlando Health (FWA 00000384)

**Protocol Title:** Barriers to Timely Administration of Thrombolytics in Acute Ischemic Stroke Patients

Under federal guidelines for expedited review, I have reviewed and approved the Expedited Review Request application and protocol dated 4/25/2012 for your project stated above. The study is approved under 21CFR 56.110 (b) (1) for this project since it presents no more than minimal risk and under Category 5 for expedited review. The waiver of informed consent is approved under 45 CFR 46.116 (d) and 45CFR 46.117(C)(2) for this project since it presents no more than minimal risk and protected health information will be de-identified. The Chair has approved this study at all Orlando Health, Inc. facilities and your office. The Institutional Review Board review process is in compliance with GCP's and included review of potential risks to subjects, risk benefit ratio, subject selection criteria and safety, content of the informed consent, confidentiality and appropriate safeguards. The project was reviewed in detail on 4/27/2012. It will be sent to the 6/7/2012 Institutional Review Board meeting and be reviewed by a majority of membership with quorum present.

Subjects may be enrolled in your project from the date of this letter through 4/26/2013. For approval to be extended after that date, a continuing review report must be submitted to the Institutional Review Board meeting prior to the deadline date. A form for continuing review is available on the IRB website (click "For Medical Professionals") at [www.orlandohealth.com](http://www.orlandohealth.com). If you wish to terminate your project before the expiration date, please notify the IRB office at 321-841-5895.

8-140



1414 Kuhl Ave.  
Orlando, FL 32806  
321.843.7000

orlandohealth.com

**Joseph**

**1205104**

**Page Two**

Institutional Review Board approval is based upon:

1. Per the guidelines for expedited review and approval, you may begin enrollment as of the date of this letter. However, enrollment may not continue after the expiration date. This expedited information will be submitted to the Institutional Review Board for final review.
2. Modifications to protocol must be approved prior to implementation unless they reduce immediate danger to subject.
3. All protocol deviations must be reported to Institutional Review Board within 5 working days.
4. FDA requires you to notify the IRB of any change of Investigator or site location, amendment or changes in the protocol, significant protocol deviations, or termination of the study. Please note that you must submit all protocol amendments to the Chairman, prior to implementing the amendment.

If you have any questions, please feel free to contact the IRB Office at 321-841-5895.

Sincerely,

John T. Promes, M.D.  
Chairman, ORMC Institutional Review Board



## LIST OF REFERENCES

- Adams, H., del Zoppo, G., Alberts, M., Bhatt, D., Brass, L., Furlan, A., & ... Wijdicks, E. (2007). Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation*, 115(20), e478-e534. Retrieved from EBSCOhost.
- Albers, G., Bates, V., Clark, W., Bell, R., Verro, P., & Hamilton, S. (2000). Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA: The Journal Of The American Medical Association*, 283(9), 1145-1150. Retrieved from EBSCOhost.
- American Heart Association. (2011). *Get with the guidelines- stroke overview*. Retrieved from <http://www.heart.org/HEARTORG/HealthcareResearch>.
- Bradley, E., Curry, L., Webster, T., Mattera, J., Roumanis, S., Radford, M., & ... Krumholz, H. (2006). Achieving rapid door-to-balloon times: how top hospitals improve complex clinical systems. *Circulation*, 113(8), 1079-1085.
- Brown, D. L., Boden-Albala B., Langa, K. M., Lisabeth, L. D., &.... Morgenstern, L.B. (2006). Projected costs of ischemic stroke in the United States. *Neurology*, 67,1390 –1395.
- Carter-Jones, C. (2011). Stroke thrombolysis: Barriers to implementation. *International Emergency Nursing*, 19(1), 53-57. Retrieved from EBSCOhost.

- Center for Disease Control and Prevention. (2011). *Data and statistics: center for heart disease and stroke prevention*. Retrieved from [http://www.cdc.gov/dhdsp/data\\_statistics/index.htm](http://www.cdc.gov/dhdsp/data_statistics/index.htm).
- Chowdhury, M., Birns, J., Rudd, A., & Bhalla, A. (2012). Telemedicine versus face-to-face evaluation in the delivery of thrombolysis for acute ischaemic stroke: a single centre experience. *Postgraduate Medical Journal*, 88(1037), 134-137.
- Crocco, T. J., Tadross, A., & Kothari, R. U. (2009). Stroke. In P. Rosen & R. Barkin (Eds.), *Rosen's Emergency Medicine* (p. ). Retrieved from <http://www.mdconsult.com.ezproxy.lib.ucf.edu/books/>.
- Dirks, M., Niessen, L., Huijsman, R., van Wijngaarden, J., Minkman, M., Franke, C., & ... Dippel, D. (2007). Promoting Acute Thrombolysis for Ischaemic Stroke (PRACTISE). *International Journal Of Stroke: Official Journal Of The International Stroke Society*, 2(2), 151-159. Retrieved from EBSCOhost.
- Dirks, M., Niessen, L., Huijsman, R., van Wijngaarden, J., Minkman, M., Franke, C., & ... Dippel, D. (2007). Promoting Acute Thrombolysis for Ischaemic Stroke (PRACTISE). *International Journal Of Stroke: Official Journal Of The International Stroke Society*, 2(2), 151-159. Retrieved from EBSCOhost.
- Fonarow, G., Smith, E., Saver, J., Reeves, M., Bhatt, D., Grau-Sepulveda, M., & ... Schwamm, L. (2011a). Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. *Circulation*, 123(7), 750-758. Retrieved from EBSCOhost.

- Fonarow, G., Smith, E., Saver, J., Reeves, M., Hernandez, A., Peterson, E., & ... Schwamm, L. (2011b). Improving door-to-needle times in acute ischemic stroke: the design and rationale for the American Heart Association/American Stroke Association's Target: Stroke initiative. *Stroke; A Journal Of Cerebral Circulation*, 42(10), 2983-2989.
- Ferrari, J., Knoflach, M., Kiechl, S., Willeit, J., Matosevic, B., Seyfang, L., & Lang, W. (2010). Stroke thrombolysis: having more time translates into delayed therapy: data from the Austrian Stroke Unit Registry. *Stroke; A Journal Of Cerebral Circulation*, 41(9), 2001-2004. Retrieved from EBSCOhost.
- Furlan, A. J. (1997). *NINDS: stroke proceedings: Furlan overview* . Retrieved from [http://www.ninds.nih.gov/news\\_and\\_events/proceedings/stroke\\_proceedings/furlan.htm](http://www.ninds.nih.gov/news_and_events/proceedings/stroke_proceedings/furlan.htm).
- Gomez, C., Malkoff, M., Sauer, C., Tulyapronchote, R., Burch, C., & Banet, G. (1994). Code stroke. An attempt to shorten in-hospital therapeutic delays. *Stroke; A Journal Of Cerebral Circulation*, 25(10), 1920-1923.
- Johnson, M., & Bakas, T. (2010). A review of barriers to thrombolytic therapy: implications for nursing care in the emergency department. *The Journal Of Neuroscience Nursing: Journal Of The American Association Of Neuroscience Nurses*, 42(2), 88-94. Retrieved from EBSCOhost.
- Hacke, W., Kaste, M., Bluhmki, E., Brozman, M., Dávalos, A., Guidetti, D., & ... Toni, D. (2007). Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *The New England Journal Of Medicine*, 359 (13), 1317-29.
- Hacke, W., Donnan, G., Fieschi, C., Kaste, M., von Kummer, R., Broderick, J., & ... Hamilton, S. (2004). Association of outcome with early stroke treatment: pooled analysis of

- ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*, 363(9411), 768-774.  
Retrieved from EBSCOhost.
- Keskin, O., Kalemoglu, M., & Ulusoy, R. E. (2005). A clinical investigation into prehospital and emergency department delays in acute stroke care. *Medical Principles and Practice*, 2005(14), 408-412.
- Kidwell, C., Alger, J., & Saver, J. (2003). Beyond mismatch: evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging. *Stroke; A Journal Of Cerebral Circulation*, 34(11), 2729-2735. Retrieved from EBSCOhost.
- Kwan, J., Hand, P., & Sandercock, P. (2004). A systematic review of barriers to delivery of thrombolysis for acute stroke. *Age And Ageing*, 33(2), 116-121. Retrieved from EBSCOhost.
- Lansberg, M., Schrooten, M., Bluhmki, E., Thijs, V., & Saver, J. (2009). Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. *Stroke; A Journal Of Cerebral Circulation*, 40(6), 2079-2084. Retrieved from EBSCOhost.
- Lau, A., Soo, Y., Graham, C., Woo, W., Wong, E., Leung, H., & ... Leung, T. (2010). An expedited stroke triage pathway: the key to shortening the door-to-needle time in delivery of thrombolysis. *Hong Kong Medical Journal = Xianggang Yi Xue Za Zhi / Hong Kong Academy Of Medicine*, 16(6), 455-462. Retrieved from EBSCOhost.
- Lindsberg, P., Häppölä, O., Kallela, M., Valanne, L., Kuisma, M., & Kaste, M. (2006). Door to thrombolysis: ER reorganization and reduced delays to acute stroke treatment. *Neurology*, 67(2), 334-336. Retrieved from EBSCOhost.

- Marler, J., Tilley, B., Lu, M., Brott, T., Lyden, P., Grotta, J., & ... Kwiatkowski, T. (2000). Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology*, 55(11), 1649-1655. Retrieved from EBSCOhost.
- Oliveira-Filho, J., & Samuels, O. (2011). *Reperfusion therapy for acute ischemic stroke*. Retrieved from <http://www.uptodate.com>.
- Roger, V., Go, A., Lloyd-Jones, D., Adams, R., Berry, J., Brown, T., & ... Wylie-Rosett, J. (2011). Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation*, 123(4), e18-e209. Retrieved from EBSCOhost.
- Romano, J., Muller, N., Merino, J., Forteza, A., Koch, S., & Rabinstein, A. (2007). In-hospital delays to stroke thrombolysis: paradoxical effect of early arrival. *Neurological Research*, 29(7), 664-666. Retrieved from EBSCOhost.
- Rivera-Bou, W. L., Cabanas, J. G., & Villanueva, S. E. (2011). *Thrombolytic therapy in emergency medicine*. Retrieved from <http://emedicine.medscape.com/article/811234-overview#aw2aab6b7>.
- Samsa, G., Matchar, D., Goldstein, L., Bonito, A., Duncan, P., Lipscomb, J., & ... Weinberger, M. (1998). Utilities for major stroke: results from a survey of preferences among persons at increased risk for stroke. *American Heart Journal*, 136(4 Pt 1), 703-713. Retrieved from EBSCOhost.
- Saver, J., Smith, E., Fonarow, G., Reeves, M., Zhao, X., Olson, D., & Schwamm, L. (2010). The "golden hour" and acute brain ischemia: presenting features and lytic therapy in >30,000 patients arriving within 60 minutes of stroke onset. *Stroke; A Journal Of Cerebral Circulation*, 41(7), 1431-1439. Retrieved from EBSCOhost.

- Saver, J. (2006). Time is brain--quantified. *Stroke; A Journal Of Cerebral Circulation*, 37(1), 263-266. Retrieved from EBSCOhost.
- Schwamm, L., Pancioli, A., Acker, J., Goldstein, L., Zorowitz, R., Shephard, T., & ... Adams, R. (2005). Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems. *Stroke; A Journal Of Cerebral Circulation*, 36(3), 690-703.
- Schestatsky, P., & Picon, P. (2005). Reasons for exclusion from thrombolytic therapy following acute ischemic stroke. *Neurology*, 65(11), 1844; author reply 1844. Retrieved from EBSCOhost.
- Strbian, D., Soenne, L., Sairanen, T., Happola, O., Lindsberg, P. J., Tatlisumak, T., & Kaste, M. (2010). Ultraearly thrombolysis in acute ischemic stroke is associated with better outcome and lower mortality. *Stroke*, 41(4), 712-716.
- The Joint Commission. (2011). Advanced certification for primary stroke centers. Retrieved from [http://www.jointcommission.org/certification/primary\\_stroke\\_centers.aspx](http://www.jointcommission.org/certification/primary_stroke_centers.aspx).
- Towfighi, A., & Saver, J. (2011). Stroke declines from third to fourth leading cause of death in the United States: historical perspective and challenges ahead. *Stroke; A Journal Of Cerebral Circulation*, 42(8), 2351-2355. Retrieved from EBSCOhost.
- Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. (1995). *The New England Journal Of Medicine*, 333(24), 1581-1587. Retrieved from EBSCOhost.

Tveiten, A., Mygland, A., Ljøstad, U., & Thomassen, L. (2009). Intravenous thrombolysis for ischaemic stroke: short delays and high community-based treatment rates after organizational changes in a previously inexperienced centre. *Emergency Medicine Journal: EMJ*, 26(5), 324-326.

White-Bateman, S., Schumacher, H., Sacco, R., & Appelbaum, P. (2007). Consent for intravenous thrombolysis in acute stroke: review and future directions. *Archives Of Neurology*, 64(6), 785-792. Retrieved from EBSCOhost.

Zivin, J. (2011). Ischemic cerebrovascular diseases. In L. Goldman & A. I. Shafer (Eds.), *Goldman's Cecil Medicine* (p. ). Retrieved from <http://www.mdconsult.com.ezproxy.lib.ucf.edu/books/>