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**Dosage Calculation for Intravenous Thrombolysis  
Of Ischemic Stroke:  
To Weigh or to Estimate?**

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*Meinem Vater, meiner Mutter und meine Ehefrau  
In Dankbarkeit gewidmet.*

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# Abstract (English)

## Background:

Estimation is a widely used method of assessing the weight of patients with acute stroke. Because the dosage of tissue plasminogen activator (tPA) is weight-dependent, errors in estimation lead to incorrect dosing.

## Methods:

We installed a ground-level scale in the computed tomography (CT) suite of our hospital and integrated a scale into the CT table of our Mobile Stroke Unit in order to prospectively assess the differences between reported, estimated, and measured weights of acute stroke patients. An independent rater asked patients to report their weight. The patients' weights were also estimated by the treating physician and measured with a scale. Differences between reported, estimated, and measured weights were analyzed statistically.

## Results:

For 100 consecutive patients, weighing was possible without treatment delays. Weights estimated by the physician diverged from measured weights by 10% or more for 27 patients and by 20% or more for 6 patients. Weights reported by the patient diverged from measured weights by 10% or more for 12 patients. Weights reported by the patients differed significantly less from measured weights (mean,  $4.1 \pm 3.1$  kg) than did weights estimated by the physician ( $5.7 \pm 4.4$  kg;  $p = 0.003$ ).

## Conclusion:

This first prospective study of weight assessment in acute stroke shows that the use of an easily accessible scale makes it feasible to weigh patients with acute stroke without the treatment delay associated with additional patient transfers. Physicians' estimates of patients' weights demonstrated substantial aberrations from measured weights. Avoiding these deviations would improve the accuracy of tPA dosage.

# Abstract (Deutsch)

## Hintergrund:

Die Schätzung ist eine weit häufig benutzte Methode zur Beurteilung des Gewichts von Patienten mit akutem Schlaganfall. Da die Dosierung von Gewebefibrinolyse (tPA) gewichtsabhängig ist, führen Schätzfehler zu falschen Dosierungen.

## Methoden:

Wir installierten eine Bodenwaage in der Computertomographie-Suite (CT) unseres Krankenhauses und bauten eine Waage in die CT-Tabelle unserer Mobile Stroke Unit ein, um die Unterschiede zwischen den berichteten, geschätzten und gemessenen Gewichten von Patienten mit akutem Schlaganfall prospektiv zu bewerten. Ein unabhängiger Bewerter bat die Patienten, ihr Gewicht anzugeben. Das Gewicht der Patienten wurde ebenfalls vom behandelnden Arzt geschätzt und mit einer Skala gemessen. Die Unterschiede zwischen berichteten, geschätzten und gemessenen Gewichten wurden statistisch analysiert.

## Ergebnisse:

Bei 100 aufeinanderfolgenden Patienten war ein Wiegen ohne Behandlungsverzögerungen möglich. Die vom Arzt geschätzten Gewichte weichen bei 27 Patienten um 10% oder mehr und bei 6 Patienten um 20% oder mehr ab. Die vom Patienten berichteten Gewichte weichen bei 12 Patienten um 10% oder mehr vom gemessenen Gewicht ab. Die von den Patienten angegebenen Gewichte unterschieden sich signifikant weniger von den gemessenen Gewichten (Mittelwert  $4,1 \pm 3,1$  kg) als die vom Arzt geschätzten Gewichte ( $5,7 \pm 4,4$  kg;  $p = 0,003$ ).

## Schlussfolgerung:

Diese erste prospektive Studie zur Gewichtsbewertung bei akutem Schlaganfall zeigt, dass die Verwendung einer leichten zugänglichen Waage das Wiegen von Patienten mit akutem Schlaganfall ohne die mit zusätzlichen Patiententransfers verbundene Behandlungsverzögerung möglich macht. Die Schätzungen der Ärzte zum Gewicht der Patienten zeigten erhebliche Abweichungen von den gemessenen Gewichten. Das Vermeiden dieser Abweichungen würde die Genauigkeit der tPA-Dosierung verbessern.

# Abbreviation list:

<b>CNS</b>	central nervous system	<b>ICH</b>	intracerebral hemorrhage
<b>SAH</b>	subarachnoid hemorrhage		
<b>BC</b>	Before Christ	<b>TIA</b>	transient ischemic attack
<b>WHO</b>	World Health Organization	<b>NIHSS</b>	National Institute of Health Stroke Scale
<b>CNS</b>	Canadian Neurological Scale	<b>MCANS</b>	Middle Cerebral Artery Neurological Score
<b>mRS</b>	modified Rankin Scale	<b>CBF</b>	cerebral blood flow
<b>SEP</b>	somatosensory evoked potentials	<b>EEG</b>	electroencephalogram
<b>ATP</b>	adenosine triphosphate	<b>ADC</b>	apparent diffusion coefficient
<b>IV</b>	intravenous	<b>CT</b>	Computer tomography
<b>rtPA</b>	recombinant tissue plasminogen activator	<b>TPA</b>	Tissue plasminogen activator
<b>MR</b>	magnetic resonance	<b>cDNA</b>	Complementary Desoxyribonucleinacid
<b>SK</b>	streptokinase	<b>UK</b>	Urokinase
<b>PAI</b>	plasminogen activator inhibitor	<b>FDP</b>	fibrin degradation product
<b>AIS</b>	Acute ischemic stroke	<b>CI</b>	confidence interval
<b>MSU</b>	mobile stroke unit	<b>IVT</b>	intravenous thrombolysis
<b>IBM</b>	Index body mass	<b>n</b>	number
<b>kg</b>	Kilogram	<b>mg</b>	milligram
<b>EUR</b>	euro	<b>USD</b>	United states Doller
<b>MRI</b>	Magnetic Resonance Imaging	<b>PET</b>	Positron-emission tomography



# 1 Introduction

## 1.1 Stroke

### 1.1.1 Definition

Stroke is an acute neurological dysfunction caused by acute focal injury of the central nervous system (CNS) attributed to a vascular cause together with cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH).

Worldwide stroke is a major cause of disability and death.

Despite its global impact in clinical research, or in assessments of the public health, the term “stroke” is not consistently defined in clinical practice.

Due to the development in basic science, neuropathology, and neuroimaging we have improved our understanding of ischemia, infarction, and hemorrhage in the CNS.

Based upon the underlying pathological mechanism, there are several types of stroke, and classifying strokes correctly is fundamental for correct treatment of patients.

This summarized in Table1 represents the final expert consensus.

**Table 1. Definition of Stroke**

The term “stroke” should be broadly used to include all of the following:

**Definition of CNS infarction:** CNS infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on

1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or
2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting  $\geq 24$  hours or until death, and other etiologies excluded. (Note: CNS infarction includes hemorrhagic infarctions, types I and II; see “Hemorrhagic Infarction.”)

**Definition of ischemic stroke:** An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. (Note: Evidence of CNS infarction is defined above.)

**Definition of silent CNS infarction:** Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.

**Definition of intracerebral hemorrhage:** A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

(Note: Intracerebral hemorrhage includes parenchymal hemorrhages after CNS infarction, types I and II—see “Hemorrhagic Infarction.”)

**Definition of stroke caused by intracerebral hemorrhage:** Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

**Definition of silent cerebral hemorrhage:** A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.

**Definition of subarachnoid hemorrhage:** Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord).

**Definition of stroke caused by subarachnoid hemorrhage:** Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

**Definition of stroke caused by cerebral venous thrombosis:** Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.

**Definition of stroke, not otherwise specified:** An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting  $\geq 24$  hours or until death, but without sufficient evidence to be classified as one of the above.

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CNS indicates central nervous system.

Table 1: Definition of Stroke (1) (Stork 2013).

## 1.1.2 . History of Definition of Stroke

The term “stroke” was first introduced into medicine in 1689 by William Cole in A Physico-Medical Essay Concerning the Late Frequencies of Apoplexies. (2). Before that “apoplexy” was used by Hippocrates circa 400 BC to describe very acute nontraumatic brain injuries. For >2000 years, neurologists sought to find the exact definition of term “stroke.” (3).

The term “transient ischemic attack” has been used by neurologists since the 1950s, to define the temporary vascular-related episodes of brain dysfunction which could not qualify as strokes.

Neurologists sought to arrive a generally consensus definitions of stroke and TIA because of great advance of information about the brain and its function, anatomy, and blood supply during the past 200 years. Physicians and other specialists in brain diseases have increased their understanding during the past 55 years. During the past 35 years, the ability to safely and quickly image the brain and its blood-supplying vessels in patients has become a reality. And, in the past 15 years, modern vascular and brain imaging has become available in most hospitals.

The current World Health Organization definition of stroke “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” was first used in 1970. (4).

An updated definition is required because of the great advance in knowledge about the nature, timing, clinical recognition of stroke since this definition was formulated.

In the Second Princeton Cerebrovascular Disease Conference in 1957, C.M. Fisher presented an extensive characterization for what he termed “transient ischemic

attacks,” that “may last from a few seconds up to several hours, the most common duration being a few seconds up to 5 or 10 minutes”. (5).

During the Fourth Princeton Cerebrovascular Disease Conference in 1965, the term “transient ischemic attack” was announced as the preferred term for temporary episodes of brain and eye ischemia. (6).

The definition of transient ischemic attacks as “episodes of temporary and focal dysfunction of vascular origin, which are variable in duration, commonly lasting from 2 to 15 minutes, but occasionally lasting as long as a day (24 hours). They leave no persistent neurological deficit” was published in 1975, an Ad Hoc Committee on Cerebrovascular Disease. (7).

When this definition of transient ischemic attack with 24 hours of symptom duration in 1975 was published, the diagnostic techniques that could determine the presence of brain infarction, and effective treatments of brain ischemia were not established.

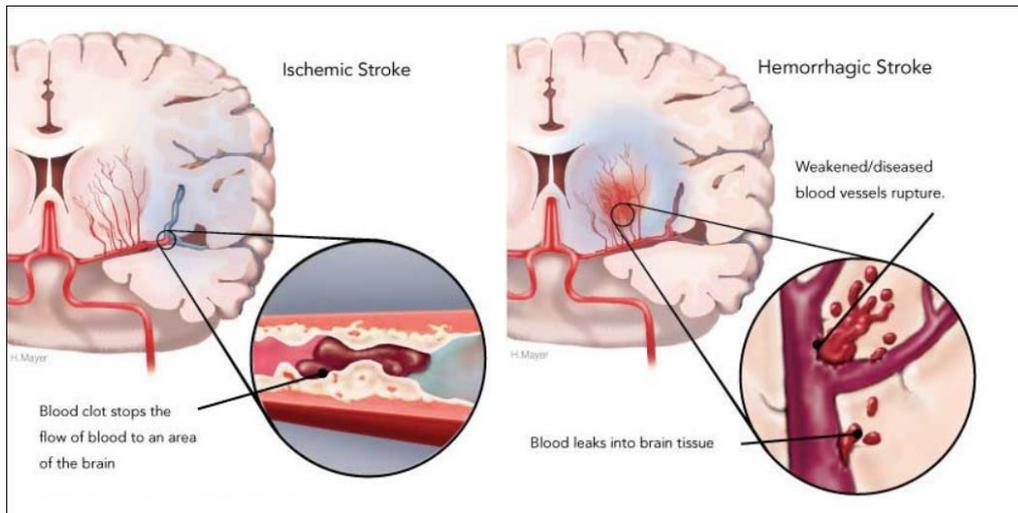


Figure 1: different types of stroke; Hemorrhage and ischemic stroke (Canada 2013).

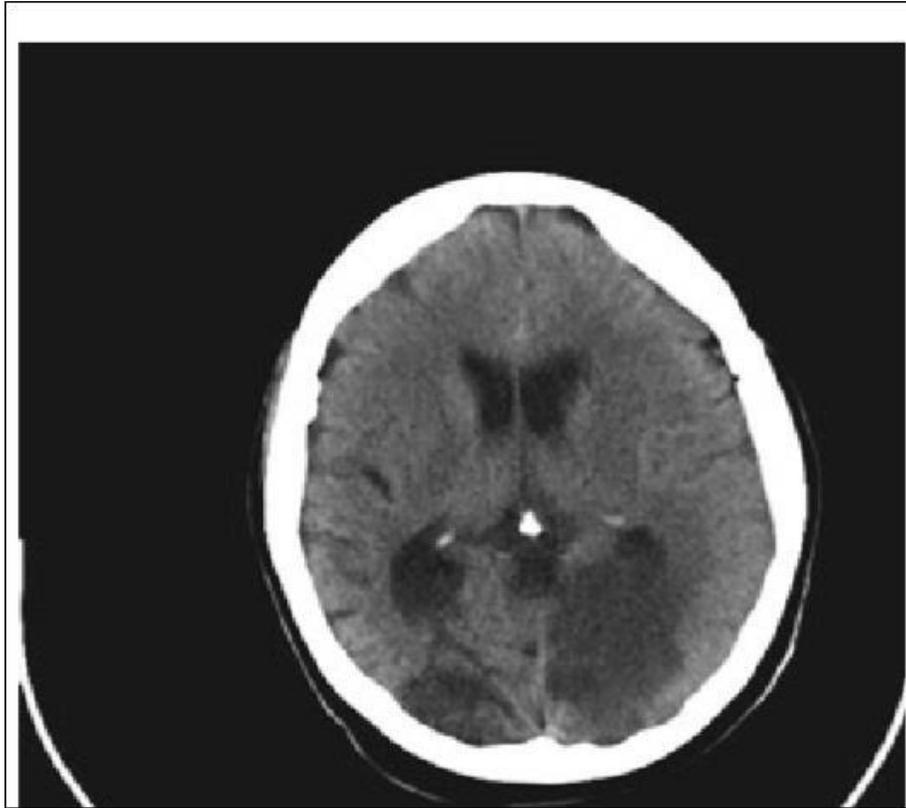


Figure 2: CT: Bilateral, extensive posterior infarcts. (Neurology 2016)

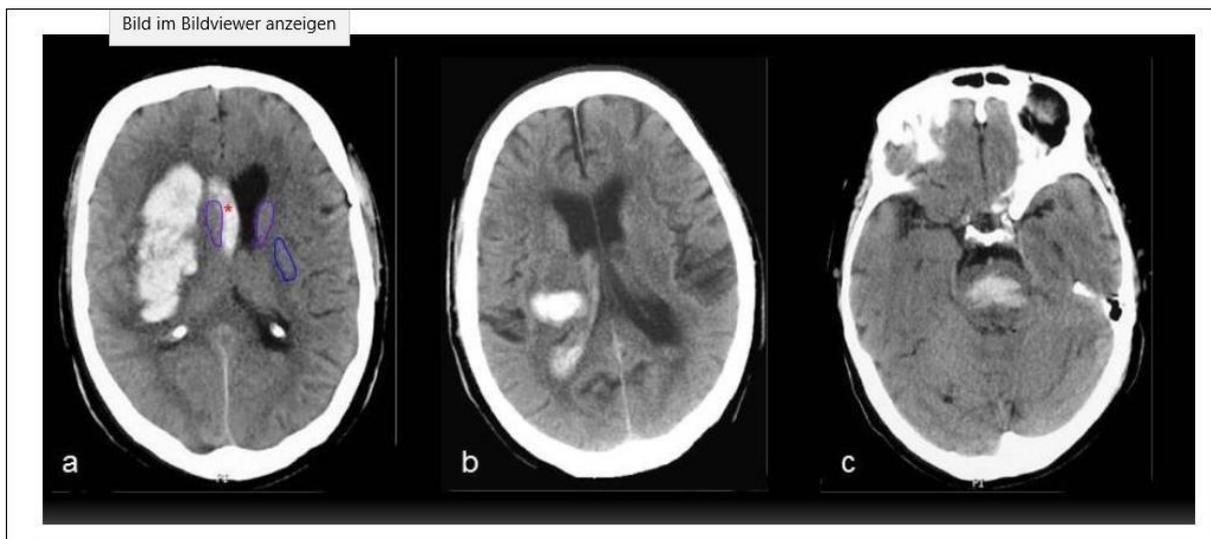


Figure 3: CT: intracerebral hemorrhage in hypertension in typical locations.( Neurology 2016).

### **1.1.3 General overview**

Stroke is one of the most common and expensive diseases. Stroke is more common in most countries today than heart attacks. Nevertheless, the level of knowledge about the stroke is much less pronounced than for other diseases.

Public awareness and presence in the media are accordingly limited.

Every stroke is an emergency but it has not always been treated as such in the past.

In most internal emergency departments, the stroke patient has often a lower priority compared to heart attack, trauma, acute abdomen, epileptic seizure or acute psychosis. (8).

Since effective acute therapies have become available, the acute stroke patient receives higher priority.

Stroke is the most common disease in most neurological clinics. Up to 50% of all inpatients in these clinics have a vascular disease of the nervous system.

As in other fields of modern medicine, advances in diagnosis and therapy have greatly changed the care structure. Patients come to the clinic more quickly, are diagnosed as an emergency and treated at modern stroke units.

There are effective treatments and the prognosis is much better than it was 10 years ago.

Stroke Units developed in Germany more than in any other region of the world. There are more than 250 Stroke Units in Germany.

There is hardly an area of clinical medicine that is so strongly influenced by German specialists internationally (9).

## 1.1.4 Epidemiology

Stroke is one of the most common diseases worldwide, the leading cause of permanent disability and, from a medical-economic perspective, among the most expensive diseases in Western industrialized countries. (10).

Worldwide, stroke is behind infectious diseases but still ahead of cancer and other cardiovascular diseases, as a cause of death. It is the leading cause of death in China, India, Russia and Brazil. (8).

According to the World Health Organization (WHO) stroke in 2016 was classified as the second leading cause of death after ischemic heart disease. More than 17 million strokes are reported worldwide and stroke is responsible for more than 6.5 million deaths each year, two thirds of them in developing countries. (11).

The incidence of cerebral infarction in Germany is approx. 220 per 100 000 inhabitants per year and transient ischemic attack (TIA) 90 per 100 000 per year, the Male to Female ratio is approximately 1.3 to 1 but from age 80 is approximately 1 to 1. Incidence increases gradually with age (from 75 years, for example, 1200 infarctions and 500 TIA / 100,000 inhabitants / year). It is expected a continuous increase of about 3% per year until the year 2050 due to demographics (12).

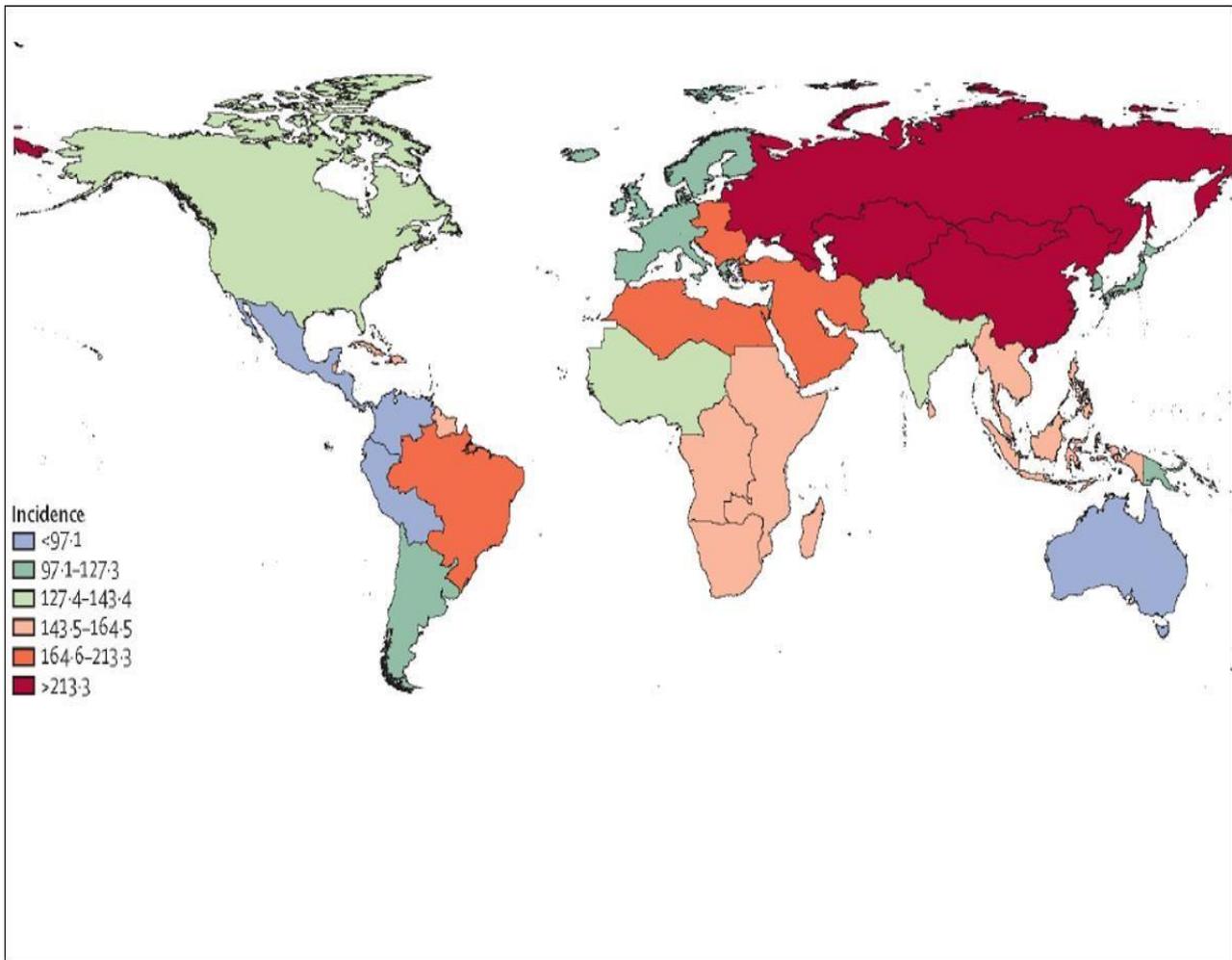


Figure 4: Incidence of Ischemic Stroke 2010. (13).

	Males	Females	total
First – time Strokes	88087	108339	196426
Repeated Strokes	29597	36492	65999
total	117684	144741	262425

Table 2: Estimated Stroke Incidence in Germany.

## 1.1.5 Outcome after stroke

In Germany, stroke is the third leading cause of death after cardiac and cancer diseases..

In 2008, the official cause of death statistics reported stroke as the cause of death in approximately 63,000 deaths.

The age-adjusted stroke mortality rates in the German population show a significant decline in men and women in recent years.

Stroke is the leading cause of acquired disability in adults (14).

Three months after the event, about 25% of surviving patients have severe limitations in activities of daily living (defined as Barthel Index <60). (Ward et al ,.2005) and ca.17% have moderate to severe dysfunctions (defined as Rankin Scale 4-5). (15).

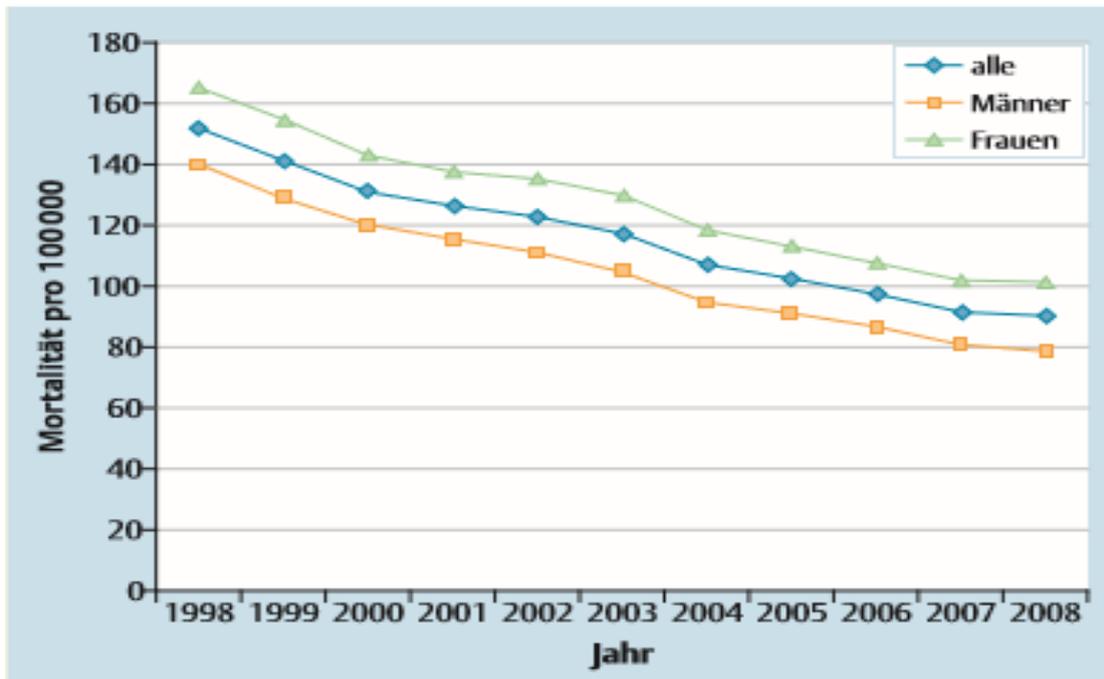


Figure 5 : Development of stroke mortality in Germany between 1998 and 2008

(official cause of death statistics Germany 2008 ([www.statistik.de](http://www.statistik.de)), directly age-standardized rates using European standard population for men and women 2008) (15).

## **1.2 Ischemic-stroke**

### **1.2.1 Prognosis**

Ischemic stroke is a major concern to the public health due to the high mortality rate and long-term disabilities that affect patients after stroke. According to published data, within 30 days of experiencing a stroke, the mortality rate is between 16% and 22% (16); this number increases to 29% within 1 year.

Furthermore, approximately 31% of patients that survive strokes need assistance in caring for themselves (17). However, the prognosis after stroke varies widely across individual patients depending on a multitude of factors that have a great impact on functional outcomes after stroke. Here, we summarize the factors that are considered independent predictors of stroke outcome.

### **1.2.2 Severity**

Stroke severity is clinically estimated based on the degree of neurological impairment, infarction location, and the size of location which are assessed by neuroimaging such as MRI and CT.

There are several ways and scales to evaluate the neurological impairment of ischemic stroke patients, because Stroke severity is a major factor in predicting the outcome of patients after stroke (18).

As an example, National Institute of Health Stroke Scale (NIHSS), Canadian Neurological Scale (CNS) and Middle Cerebral Artery Neurological Score (MCANS) are the most common scales to evaluate stroke severity and modified Rankin Scale (mRS).

NIHSS is a well-known and widely-used scale because it considers the overall degree of neurological deficits and can accurately predict the stroke outcome, especially in the first three months (19).

It has been shown in the literature that the odds of excellent outcome decrease by 17% for each additional point on the NIHSS scale (20). Moreover, it also has been shown that patients with NIHSS scale  $\leq 6$  are more likely to recover well after stroke. Patients with a score of NIHSS measured  $\geq 16$  are more like to have unfavorable outcome (21).

#### **A- Modified Rankin Scale (mRS). (22.23.24).**

The Modified Rankin Scale (mRS) is a scale used to measure the degree of disability in patients who have had a stroke, as follows:

0: No symptoms at all

1: No significant disability despite symptoms; able to carry out all usual duties and activities

2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3: Moderate disability; requiring some help, but able to walk without assistance

4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6: Dead.

**B- The National Institutes of Health Stroke Scale form used by Providence Health System (NIHHS SCORE).**

Category	Score/Description	Date/Time Initials				
1a. Level of Consciousness (Alert, drowsy, etc.)	0= Alert 1= Drowsy 2= Stuporous 3= Coma					
1b. LOC Questions (Month, age)	0= Answer both correctly 1= Answer one Correctly 2= Incorrect					
1c. LOC Commands (Open/close eyes, make fist/let go)	0= Obeys both correctly 1= Obeys one correctly 2= Incorrect					
2. Best Gaze (Eyes open – patient follows examiner’s finger or face)	0= Normal 1= Partial gaze palsy 2= Forced deviation					
3. Visual Fields (Introduce visual stimulus/ threat to pt’s visual field quadrants)	0= No visual loss 1= Partial Hemianopia 2= Complete Hemianopia 3= Bilateral Hemianopia(blind)					
4. Facial Paresis (Show teeth, raise eyebrows and squeeze eyes shut)	0= normal 1= Minor 2= partial 3= Complete					
5a. Motor Arm - Left 5b. Motor Arm – Right (Elevate arm to 90° if patient is sitting, 45° if supine)	0= No drift 1= drift 2= Can’t resist gravity 3= No effort against gravity 4=No movement X= Untestable (Joint fusion or limb amp)	Left				
		Right				
6a. Motor Leg - Left 6b. Motor Leg – Right (Elevate Leg 30° with patient supine)	0= No drift 1= Drift 2= Can’t resist gravity 3= No effort gravity 4= No movement X= Untestable (Joint fusion or limb amp)	Left				
		Right				
7. Limb Ataxia (Finger nose, heel down shin)	0= No ataxia 1= Present in one limb 2= Present in two limbs					
8. Sensory (Pin prick to face, arm, trunk and leg – compare side to side)	0= Normal 1= Partial loss 2= Severe loss					
9. Best Language (Name item, describe a Picture and read sentences)	0= No aphasia 1= Mild to moderate aphasia 2= Severe aphasia 3= Mute					
10. Dysarthria (Evaluate speech clarity by Patient repeating listed words)	0= Normal articulation 1= Mild to moderate slurring of words 2= Near to unintelligible or worse X= Intubated or other physical barrier					
11. Extinction and Inattention (Use information from prior testing to identify neglect or double)	0= No neglect 1= Partial neglect 2= Complete neglect					

simultaneous stimuli testing)						
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Table 3: American Association of Neuroscience Nurses 2006

## 1.2.3 Mechanism

There are two major mechanisms for ischemia in brain: thromboembolism and hemodynamic failure.

Thromboembolism caused by embolism or in situ thrombosis and leads to a decrease in regional cerebral blood flow (CBF).

Hemodynamic failure caused by arterial occlusion or stenosis, when collateral blood supply fail to maintain CBF at sufficient levels to preserve the brain function under some circumstances that decrease perfusion proximally to the arterial lesion (systemic hypotension or low cardiac output) and increase metabolic demands (fever, acidosis) or conditions that lead to “steal” of blood from affected to unaffected areas in the brain (carbon dioxide retention) (25).

### 1.2.3.1 Normal cerebral blood flow

Although the brain accounts for only 2% of body weight, it receives about 15% (about 1.2 l) of cardiac output in rest and consumes about 20% of the body's total O<sub>2</sub> requirement (about 3.35 ml of oxygen per 100 g of brain tissue per minute). In a healthy adult, cerebral blood flow (CBF) is approximately 60-80 ml per 100 g of brain tissue per minute.(8).

### **1.2.3.2 Cerebral blood flow changes in ischemia**

The main factors that ultimately determine the tissue outcome after vessel occlusion are regional CBF and duration of vessel occlusion.

A decrease in regional CBF leads to diminished tissue perfusion. Local perfusion pressure is the main factor that influence the eventual outcome of tissue in persistent large vessel occlusion (26) and depends on several factors such as systemic arterial pressure and the presence and extent of collaterals (as a result to loss of the ischemic brain's autoregulatory capacity).

### **1.2.3.3 Cerebral Blood Flow Thresholds in Cerebral Ischemia**

The tissue outcome following arterial occlusion varies according to the concept that CBF thresholds exist, below which neuronal integrity and function are differentially affected.

Early human studies conducted in the 1950s during carotid artery endarterectomy found that hemiparesis occurred when regional CBF fell below 50% to 30% of normal, and permanent neurologic deficit occurred if mean CBF fell below 30% of normal during clamping of carotid by using intracarotid xenon 133 injections (27).

The development of permanent neurologic sequelae is a time-dependent process.

Low cerebral blood flow are tolerated only for a short period of time, while higher cerebral blood flow need a longer time for infarction to happen. (28, 29).

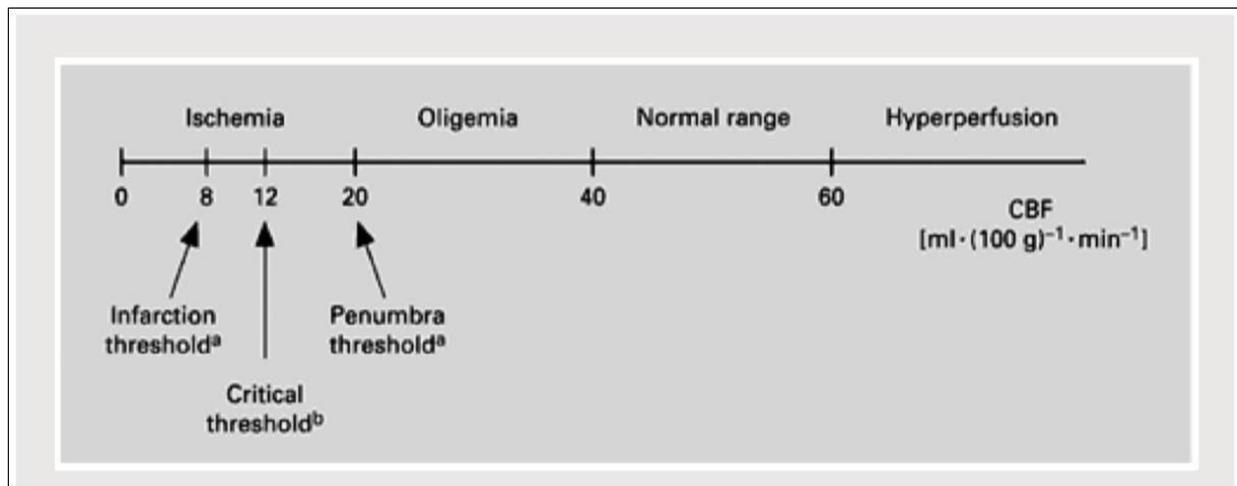


Figure 6: Schematic drawing of the different cerebral blood flow thresholds. (30).

The relationship between the cerebral blood flow threshold and focal cerebral ischemia proposed by landmark studies performed by Symon and colleagues (1977), who investigated the relationship between severity of decreased cerebral blood flow and degree of neurologic dysfunction at various durations of ischemia in a baboon model of middle cerebral artery occlusion. They proved that brain tissue perfusion between certain cerebral blood flow (22 mL/ 100 mg/min to 8 mL/100 mg/min) maintains brain tissue structural integrity and can be reversed with reperfusion even when prolonged hypoperfusion stops functioning.

1981 Johns and colleagues proved that permanent or transient neurologic deficit is time dependent, they proved that the cerebral blood flow values below which brain tissue becomes infarcted are dependent on the duration of vessel occlusion by using a temporary or permanent middle cerebral artery occlusion. (31).

#### **1.2.3.4 Concept of Ischemic Core and Ischemic Penumbra**

Astrup and colleagues (1981) first introduced the concept of ischemic core and ischemic penumbra. This concept supposes that in acute stroke, the tissue supplied by the occluded artery is compartmentalized into areas of irreversibly damaged brain tissue and areas of brain tissue that are reversibly damaged.

The ischemic core represents tissue that is irreversibly damaged. PET studies in humans suggest the ischemic core corresponds to cerebral blood flow values of less than 7 mL/100 mg/min to 12 mL/100 under a limited time (probably no longer than an hour (32, 33, 34).

The ischemic penumbra represents tissue that is functionally impaired but structurally intact and remediable. It corresponds to a high cerebral blood flow between 17 mL/100 mg/min to 22 mL/100 mg/ min and 7 mL/100 mg/min to 12 mL/100 mg/min. (35.36)

The aim of acute stroke therapy is to rescue this tissue by raising its flow to non-ischemic levels. It is proved that under normal circumstances this tissue is not at risk of infarction (26).

It is supposed that under certain circumstances, such as hypotension, fever, or acidosis, oligemic tissue can be incorporated into penumbra and develop infarction.

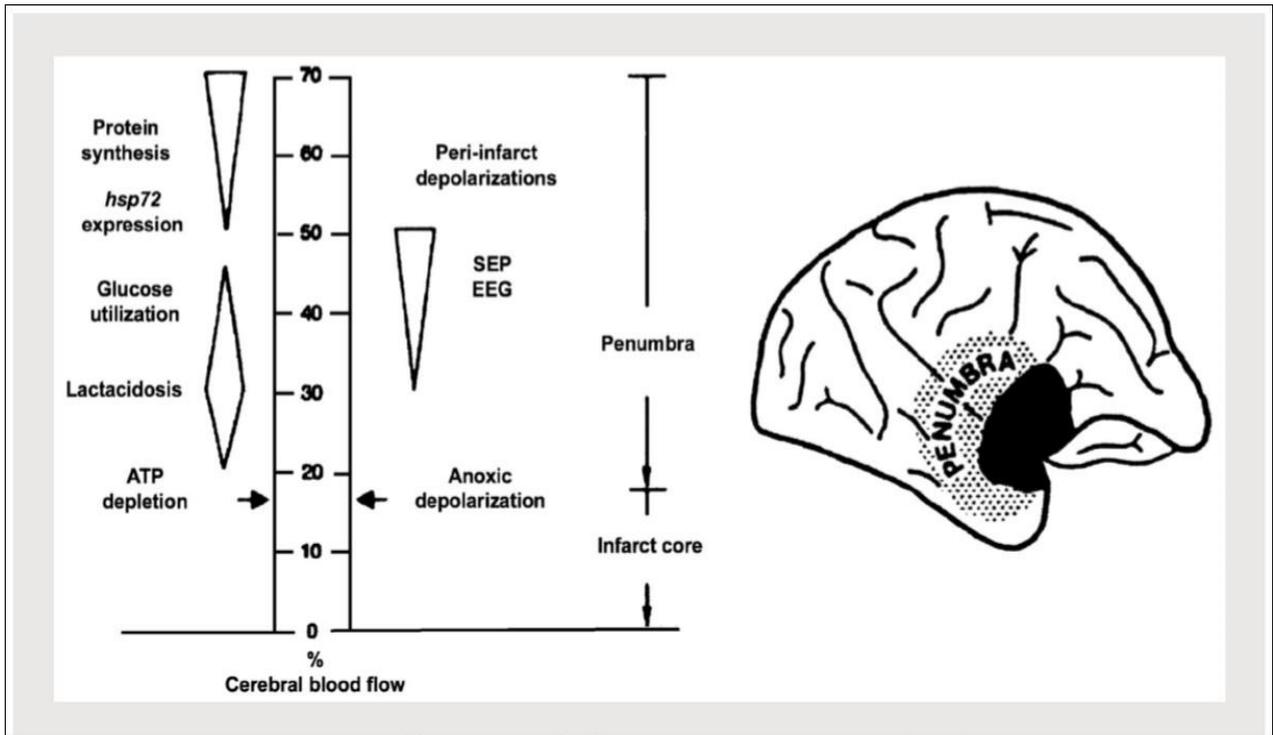
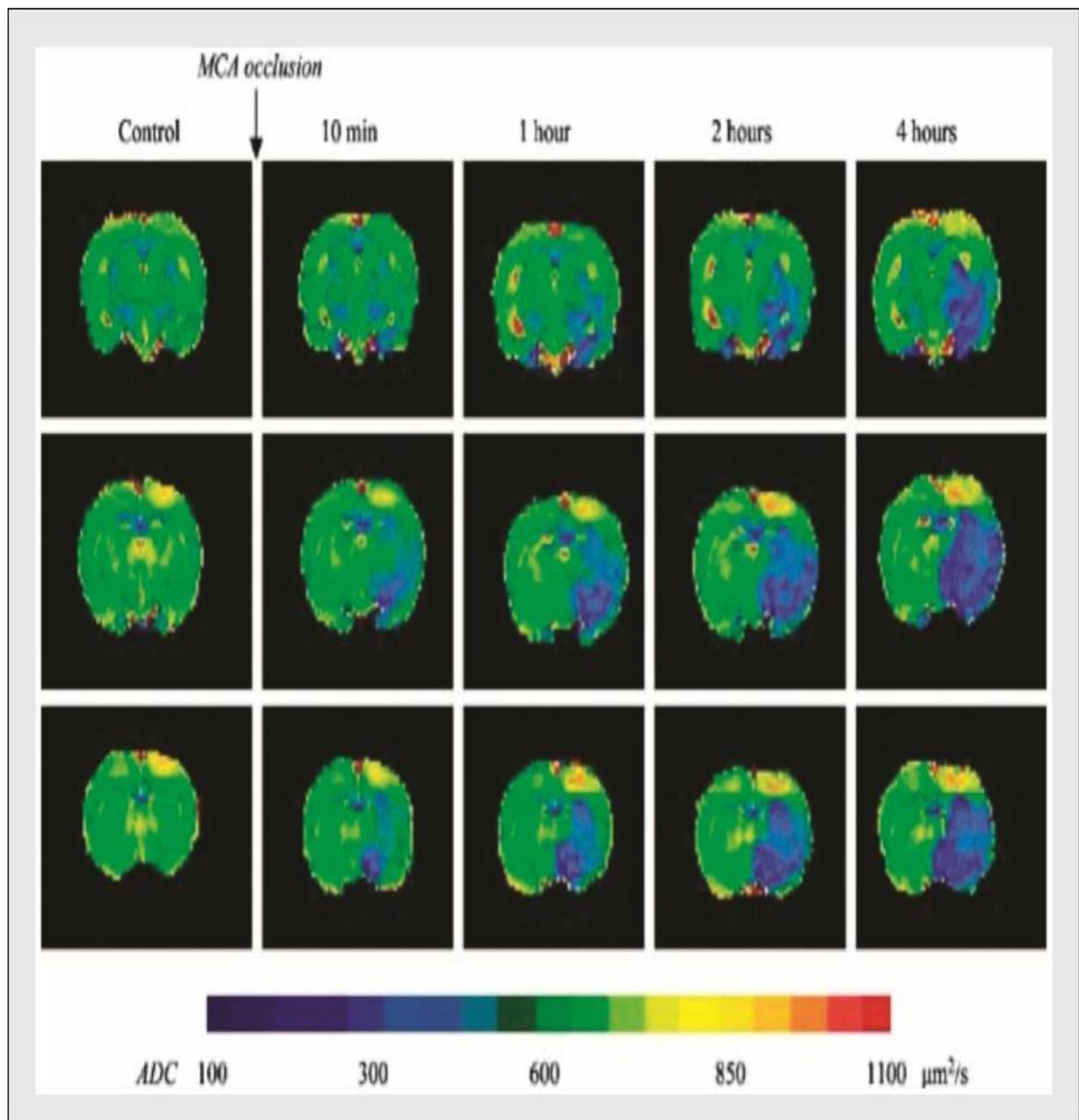


Figure 7: Thresholds of metabolic (left) and electrophysiologic (right) disturbances during gradual reduction of cortical blood flow. SEP = somatosensory evoked potentials

EEG = electroencephalogram; ATP = adenosine triphosphate. (37).



**Figure 8: Experimental model of middle cerebral artery occlusion in rats.**

Serial MRIs (coronal sections) at three levels in the brain depicting the apparent diffusion coefficient of water (ADC) (blue) demonstrating the time-dependent growth of the ischemic core. (37).

## 1.2.4 . Treatment acute ischemic Stroke

The therapy of acute ischemic stroke has been massively developed in the past 2 decades. It is possible with new treatment options to reverse ischemia und enable patients to work again whereas previous destined to severe disability or death. IV thrombolysis therapy that began 20 years ago, mechanical thrombectomy and endovascular treatment had improved outcomes in patients with severe neurologic deficits from a proximal intracranial vessel occlusion. (38).

There are three main principles of acute stroke care:

- 1) achieve timely recanalization of the occluded artery and reperfusion of the ischemic tissue.
- 2) optimize collateral flow.
- 3) avoid secondary brain injury.

Recanalization and reperfusion are the optimal therapy of acute stroke treatment to reduce infarct size and reverse neurologic deficits.

Recanalization is defined by the degree of reopening of the occluded artery. Reopening the occluded artery help to recover the hypoperfused brain tissue that is not sufficiently perfused. This tissue represents the ischemic penumbra that can be salvaged if adequate blood flow is promptly reestablished. Nowadays advanced CT perfusion or magnetic resonance (MR) diffusion/perfusion can exhibit this tissue at risk (penumbra imaging) (39). Reperfusion is measured by the degree of flow reaching the previously hypoperfused brain tissue. The two evidence-based strategies to achieve reperfusion are:

- 1-chemical thrombolysis with recombinant tissue plasminogen activator (rtPA), also known as alteplase.
- 2- mechanical embolectomy with a retrievable stent.

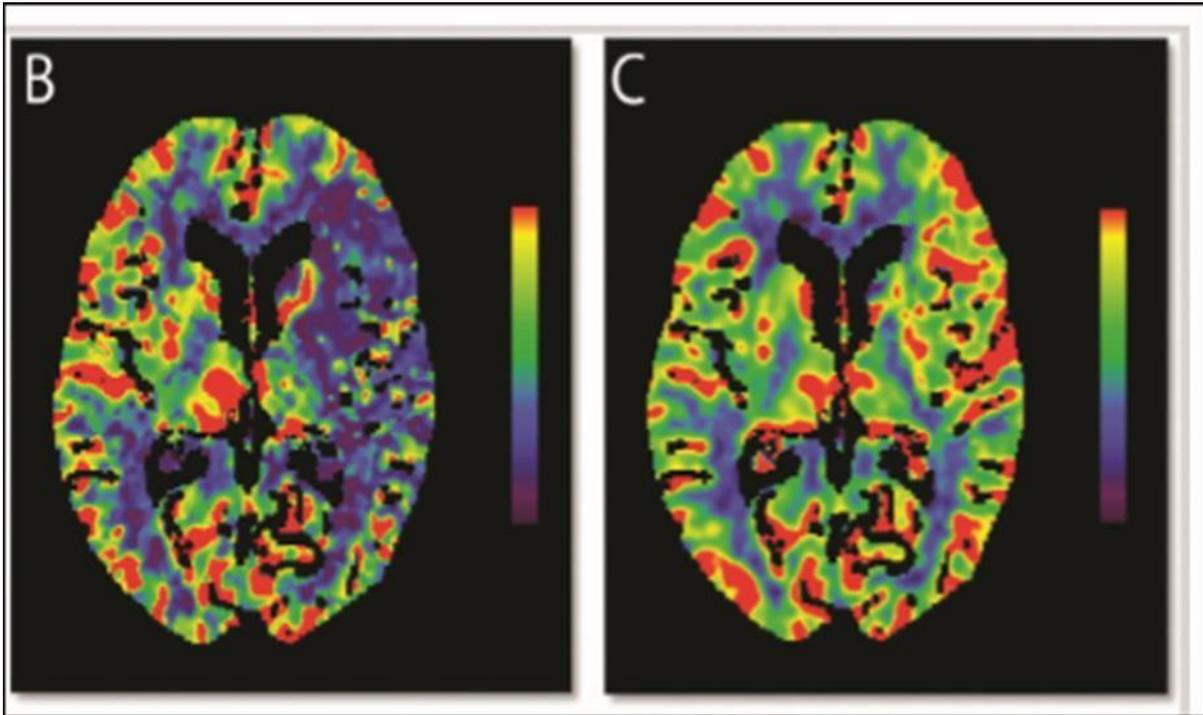


Figure 9: B: Cerebral blood flow image of the CT perfusion disclosing hypoperfusion throughout the left middle cerebral artery distribution. C, Cerebral blood volume image of the CT perfusion showing no definite areas of established infarction. (38).

# 1.3 Tissue plasminogen activator (tPA).

## 1.3.1 General Overview

tPA is a protein that helps in the breakdown of blood clots. It is a serine protease found on endothelial cells in blood vessels. tPA works as the major enzyme in catalyzing the conversion of plasminogen to plasmin and to clot breakdown. Human tPA has a molecular weight of ~70 kDa in the single-chain form. (40).

tPA was first produced by recombinant DNA techniques in 1982.

After a cDNA library was established with the use of reverse transcriptase and mRNA from human melanoma cells.

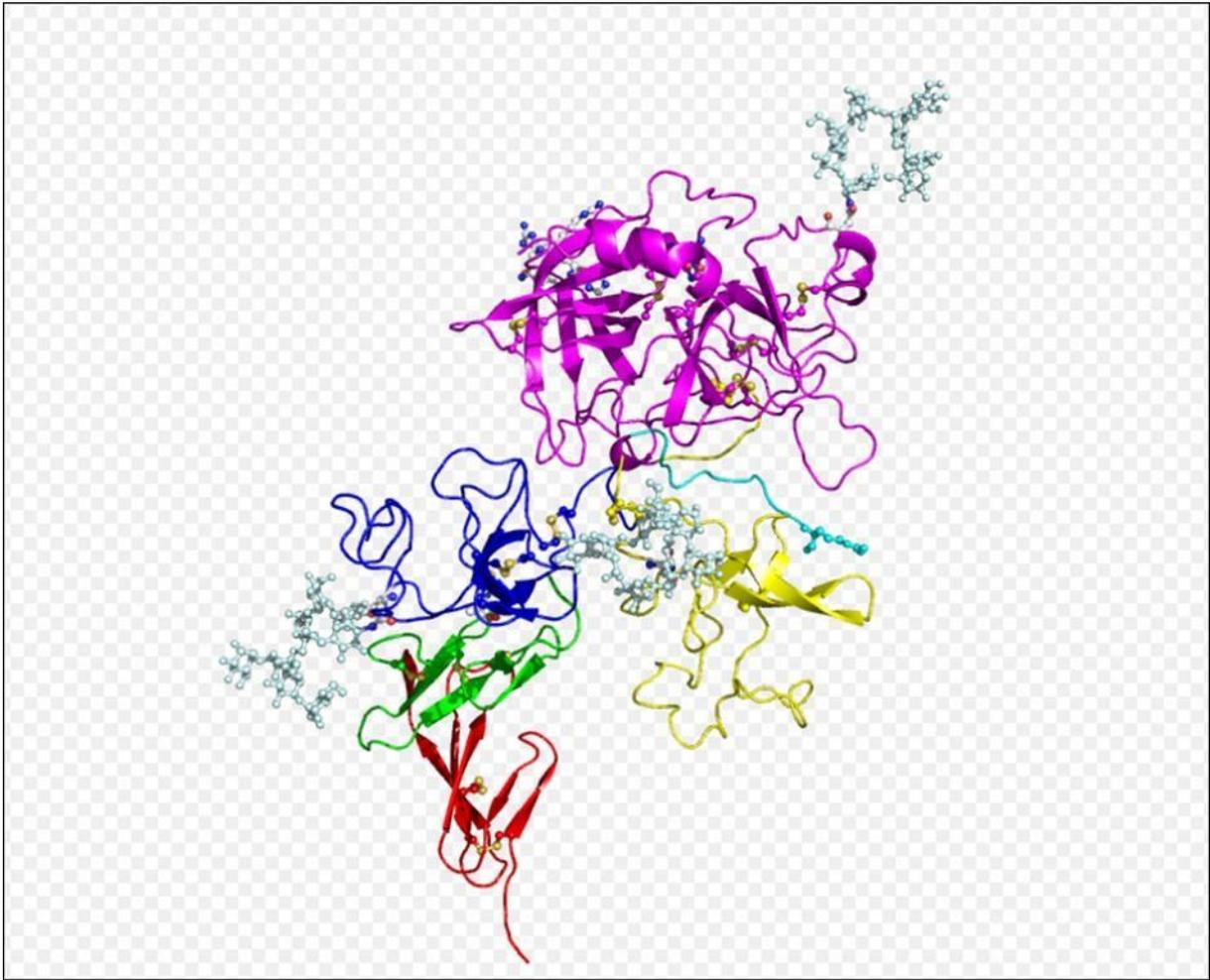
Tissue-type plasminogen activators were initially identified and isolated from mammalian tissues. (41).

tPA was the first pharmaceutical produced synthetically with the use of mammalian cells, specifically Chinese hamster ovarian cells.

Recombinant tPA is commonly referred to as r-tPA and sold under multiple brand names. (42).

In 1996 after the positive National Institute of Neurological Disorders and Stroke (NINDS)-2 trial, Recombinant t-PA (rt-PA) was approved for acute ischemic stroke, and until now is the only established choice as acute thrombolytic treatment in acute ischemic stroke. (43).

Despite the great progress in last years in imaging techniques and the introduction of stroke care units, many patients are left untreated because of the narrow time window of 4.5 hours, unknown onset, lack of awareness, and a high number of exclusion criteria for currently approved treatment. (44).



**Figure 10: A theoretical structure of the full t-PA enzyme in humans.**

Sugar residues are the light cyan-grey molecules, and the different domains are marked in different colors. (40).

## 1.3.2 Early Development of Thrombolytics

Tillett and Garner discovered in 1933 that certain strains of *Streptococcus* could dissolve fibrin clots (45). The role of fibrinogen was supposed through serendipity: streptococci agglutinated in human serum but not in plasma (46).

In 1955 Tillett proved the clinical effectiveness of streptokinase (SK) in patients with extracranial occluding vascular thrombi (47). In the 1940s, Macfarlane and Pilling discovered the fibrinolytic potential of human urine, leading to extraction of urokinase (UK), a strong activator of plasminogen to form plasmin (48).

Staphylokinase was isolated by Lack from *Staphylococcus* strains (50).

In 1958 Sussman and Fitch reported to first time about the use of a thrombolytic agent for acute ischemic stroke (51).

They treated 3 patients with intravenous plasmin (fibrinolysis) daily for 4–6 days; only 1 patient showed clinical improvement.

The early studies of treatment with thrombolytic therapy for acute ischemic stroke using either SK or UK did not exhibit a benefit, however, intra cerebral hemorrhage was a leading cause of death (52).

These led to limitations in study design and technology. After the development in imaging technology a limited number of pilot studies were performed using angiography as a diagnostic method. A placebo-controlled pilot study was conducted in 1963 by Meyer et al.

(53) This study compared the administering intravenous plasmin with placebo over 4 h daily for 3 days in 40 patients with middle cerebral artery occlusion. No differences between the both treatment groups were found.

1964 a subsequent trial in 73 patients with progressive stroke of using streptokinase plus heparin showed a higher mortality and intra cerebral hemorrhage rate than heparin alone (54).

It could be argued that intra cerebral hemorrhage could already have been present at admission, because computer tomography (CT) was first available in 1970. Later streptokinase was abandoned for the treatment of acute cerebral ischemia due to high intra cerebral hemorrhage rate (55,56).

The advances in neuro-imaging technic by CT scanning led to the initiation of new investigations in the 1980s.

Fujishima 1968 conducted a study on 143 patients treated with either urokinase or a combination of urokinase and dextran sulphate. Clinical improvement and safety of 74% was reported for urokinase and 84% for the combination (57).

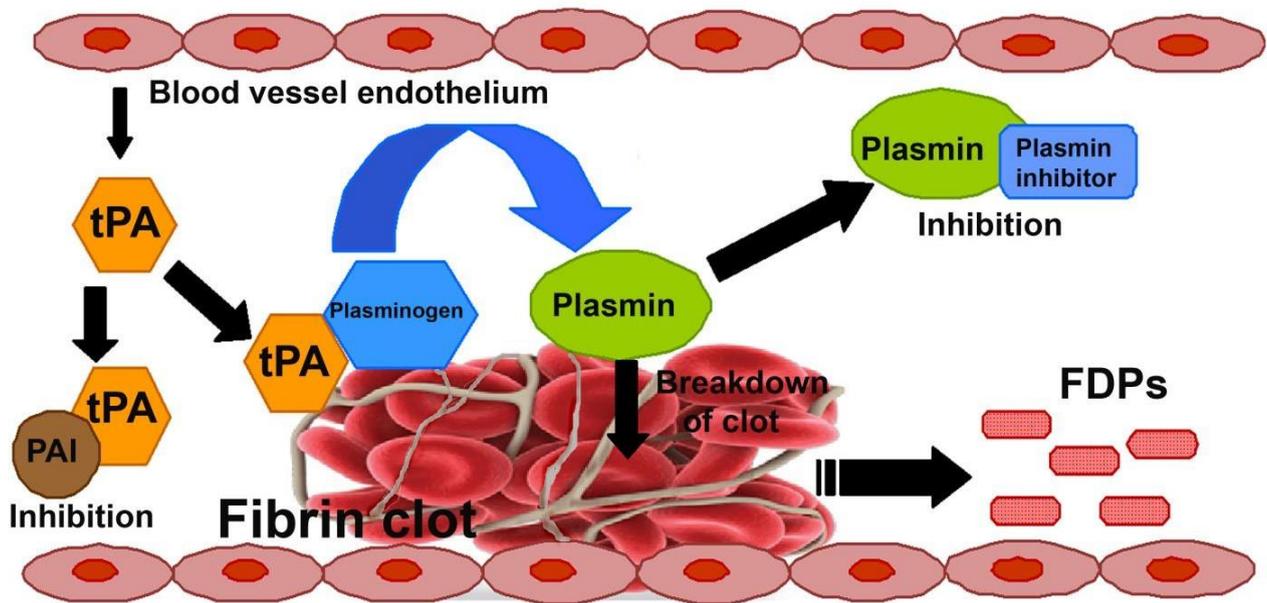


Figure 11: In vivo mechanism of action of tPA within the fibrinolytic system.

tPA can go one of three ways in the body; (1) uptake by the liver and clearance through receptors therein, (2) inhibition by a plasminogen activator inhibitor (PAI) and subsequent hepatic clearance, or (3) through the activation of plasminogen to plasmin in order to degrade fibrin to fibrin degradation products (FDP)(49).

## THROMBOLYSIS WITH FIBRINOLYSIN IN CEREBRAL ARTERIAL OCCLUSION

Bernard J. Sussman, M.D.  
and  
Thomas S. P. Fitch, M.D., Plainfield, N. J.

The most promising therapy for thrombotic occlusion of any vessel supplying the brain will probably be immediate solution of the clot by a parenterally administered agent. A surgically directed approach to the problem may be frustrated by the increasingly apparent complexities of vascular thrombosis. The appearance of symptoms may depend on complicated relationships between anastomotic channels. There is increasing evidence to make us speculate that a hemiplegia resulting from an apparent angiographically demonstrated thrombosis of the carotid artery, or of its cerebral branches, may actually result from the final thrombotic closure or stenosis of a vital collateral vessel elsewhere that is compensating for a long-standing obliterated proximal channel. Although transient neurological deficits may be related to alterations of the general systemic blood pressure, on which the stability of the collateral circulation depends, the more persistent and complete deficits are more likely the result of a final strategic thrombosis or other form of occlusion. Whatever might be done by the surgeon electively for lesser symptoms when the site of thrombosis or stenosis is demonstrable, in the presence of a severe neurological deficit, only the immediate elimination of the thrombus is likely

*Three patients with hemiplegia were treated by the slow intravenous infusion of fibrinolysin. The site of occlusion of the cerebral vessels was located in each case by arteriography. In one case the angiograms clearly showed nonfilling of the middle cerebral group of arteries before treatment, while on the eighth day after beginning treatment good filling of the middle cerebral vessels was obtained. This patient showed the most favorable results. The history of rheumatic heart disease and the fact that treatment was commenced within six hours after the onset of symptoms suggest that the lesion was caused by an embolus originating in the fibrillating left atrium and that the embolus was a fresh thrombus most susceptible to the lytic agent. No detrimental effects that could be ascribed either to the diagnostic angiography or to the administration of fibrinolysin were observed in these patients.*

Figure 12: The first publication with a thrombolytic agent in stroke (JAMA,1958), (58). Reproduced with permission by the publisher.

### **1.3.3 Tissue Plasminogen Activator**

The first study with t-PA in patients with acute myocardial infarction was reported in 1983, leading to good results with recanalization in 6 out of 7 patients (59). The dramatic development came later in that year when rt-PA was obtained by expression of the cloned gene in a mammalian cell system (60).

After the publication of the GUSTO-I trial (a study that randomized over 40,000 patients to combinations of SK or rt-PA with heparin), a large-scale use of rt-PA in acute myocardial infarction had started. This trial proved that rt-PA is superior to SK. (61).

Terashi was the first person who used rt-PA in a trial in AIS in 1990(62), 364 patients were treated with either rt-PA or urokinase. He found no differences between the two groups.

In 1992 two pilot studies, sponsored by the NINDS performed by using escalating doses of 0.35–1.08 mg/kg rt-PA in a total of 94 patients and a time window up to 3 h after onset (62,63).

The subsequent major NINDS-2 trial, published in 1995, showed that 0.9 mg/kg IV. rt-PA, administered within 3 h of symptom onset to patients with acute cerebral ischemia led to an improvement clinical outcome at 3 months compared to patients who received placebo, the risk of symptomatic intracerebral hemorrhage was 6.4% (64).

The Food and Drug Administration approved in 1995 the use of rt-PA in AIS patients depending on the outcome of the NINDS-2.

The ECASS-1/2/3, ATLANTIS-A/B and EPITHET trials investigated between 1998 and 2008 the safety and efficacy of rt-PA in acute cerebral ischemia, only the ECASS-3 reported a benefit. (65-70)

A pooled analysis, performed by Lees et al. (71) in 2010, showed a moderate benefit for rt-PA between 3 and 4.5 h, with greater benefit with earlier use. This finding was confirmed in a Canadian rt-PA registry 2011 (72, 73).

To date, rt-PA is still the only licensed thrombolytic agent for acute cerebral stroke, the dose is of 0.9 mg/kg, administered starting with an intravenous bolus of 10% of dose, followed by intravenous infusion of the rest of the dose over 60 min, according to the NINDS study criteria (64).

In 2009, the American Heart Association Stroke Council published, recommendation to treat the patients with rt-PA within the time period of 3–4.5 h after onset of ischemic stroke when additional criteria are taken into account (71). They are depending on the results of the ECASS-3 trial (66), the outcome of the pooled analysis performed by Lees et al (67), and the publications from the SITS-ISTR registry (75,76).

In 2011, rt-PA approved by the European Medical Agency for its use up to 4.5 h after onset with exclusion patients older than 80 years.

However, recent evidence supports the use of intravenous thrombolysis in patients aged over 80 years as well as in patients with diabetes and prior stroke if they otherwise fulfil treatment criteria (77,80).

The Food and Drug Administration has not extended the license time window more than 3 h. In Japan, rt-PA with low dose (0.6 mg/kg i.v.) was approved in 2005 for use up to 3 h after onset (78) , and extended to 4.5 h in 2012.

Twenty-Year history of the evolution of stroke thrombolysis with intravenous Alteplase to reduce long-term disability was published on 7. Jul. 2015 compared the result of National Institute of Neurological Disorders and Stroke (NINDS) and the 6 further randomized trials that compared tPA and placebo in various time windows 0 to 6 hours from stroke symptom onset (Table 4).

This meta-analysis proved the generalized efficacy of tPA in the 0- to 4.5-hour time window, regardless of baseline stroke severity or age, with maximal benefit with treatment time (83).

Trial	n	Time Window	Mean Age (SD)	Number Age>80	Median NIHSS	Prespecified Primary Outcome	mRS, 0-1 Overall Alteplase vs Placebo	mRS, 0-2 Overall Alteplase vs Placebo	Fatal sICH With Alteplase†
NINDS A	291	0-3	67 (11)	54	14	≥4-point reduction in NIHSS or reaching 0 at 24 h	43% vs 27%; OR, 2.0 (CI <sub>95</sub> , 1.5-2.8)‡	50% vs 38%; OR, 1.6 (CI <sub>95</sub> , 1.2-2.2)‡	2.9%
NINDS B	333	0-3	68 (13)		14.5	Composite mRS, Barthel, NIHSS, GOS			
ECASS*	620	0-6	65 (12)	0	12.5	Barthel, median mRS	36% vs 29%; OR, 1.3 (CI <sub>95</sub> , 1.0-1.9)	45% vs 40%; OR, 1.3 (CI <sub>95</sub> , 0.9-1.7)	6.1%
0-3-h subgroup	87	0-3					40% vs 24%; OR, 2.2 (CI <sub>95</sub> , 0.9-5.7)	43% vs 34%; OR, 1.4 (CI <sub>95</sub> , 0.6-3.4)	
ECASS II	800	0-6	68	0	11	mRS, 0-1	40% vs 37%; OR, 1.2 (CI <sub>95</sub> , 0.9-1.6)	54% vs 46%; OR, 1.4 (CI <sub>95</sub> , 1.1-1.8)‡	4.4%
0-3-h subgroup	158	0-3					42% vs 38%; OR, 1.2 (CI <sub>95</sub> , 0.6-2.3)	52% vs 43%; OR, 1.4 (CI <sub>95</sub> , 0.8-2.7)	
ATLANTIS A/B, 0-3 h	61	0-3	66 (11)	0	10	mRS, 0-1	48% vs 37%; OR, 1.6 (CI <sub>95</sub> , 0.5-4.5)	57% vs 50%; OR, 1.3 (CI <sub>95</sub> , 0.5-3.7)	4.2%
ATLANTIS A/B, 3-6 h	691	3-6					41% vs 43%; OR, 0.9 (CI <sub>95</sub> , 0.7-1.3)	46% vs 49%; OR, 0.9 (CI <sub>95</sub> , 0.6-1.2)	
ECASS III	821	3-4.5	65 (12)	0	9.5	mRS, 0-1	52% vs 45%; OR, 1.3 (CI <sub>95</sub> , 1.0-1.8)‡	67% vs 62%; OR, 1.2 (CI <sub>95</sub> , 0.9-1.7)	0.7%
EPITHET	100	3-6	72 (13)	25	13	Infarct growth	35% vs 24%; OR, 1.6 (CI <sub>95</sub> , 0.7-3.8)	67% vs 62%; OR, 1.2 (CI <sub>95</sub> , 0.6-2.7)	7.7%
IST3	3035	0-6	81§	1696	11	mRS, 0-2	24% vs 21%; OR, 1.2 (CI <sub>95</sub> , 1.0-1.4)	37% vs 35%; OR, 1.1 (CI <sub>95</sub> , 0.9-1.2)	3.6%
0-3-h subgroup	849	0-3					19% vs 15%; OR, 1.4 (CI <sub>95</sub> , 0.95-1.9)	31% vs 23%; OR, 1.5 (CI <sub>95</sub> , 1.1-2.0)‡	

**Table 4: Randomized Trials of Alteplase vs Placebo. (83).**

Data extracted from Cochrane systematic review (84) ATLANTIS indicates Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; CI, confidence interval; ECASS, European Cooperative Acute Stroke Study; EPITHET; Echoplanar Imaging Thrombolytic Evaluation;

\*Alteplase dose 1.1 mg/kg; all other trials 0.9 mg/kg.

Intravenous recombinant tissue plasminogen activator (rt-PA) in acute ischemic stroke is weight-based dosing. The standard dose of IV rtPA for acute ischemic stroke is 0.9 mg/kg, 10% administered as a bolus and the remainder infused over 1 hour. (85). The maximal dose should not be more than 90 mg, for that potential medication dosing errors may affect the relative risks and benefits of this therapy.

Weight is usually estimated by the patient, the family, the nurse, or the treating physician. Difference between actual and estimated weight leads to an incorrect dose and may adversely influence outcome.

## 1.4 Mobile stroke unit (MSU)

The treatment of stroke should be initiated as soon as possible because of the narrow therapeutic time window. Until now many patients still fail to reach the hospital within the narrow time window to receive maximum treatment to benefit from advanced stroke therapies, including recombinant tissue plasminogen activator (tPA) and mechanical thrombectomy. (86).

The great advance of emergency medical services, telemedicine, and mobile technology, including transportable computed tomography scanners, has presented the idea to decrease the time of therapy in acute stroke with a mobile stroke unit (MSU)(86).

The Mobile Stroke Unit MSU is an ambulance, equipped with a CT scanner and point of care laboratory unit and accompanied by a neurologist and neuroradiologist. Neurologists can directly conduct the patient's medical history the physical examination, blood sample analysis and the neuroradiologist immediately performs the CT scan. (87).

The thrombolytic therapy will directly be started by the neurologist if the inclusion and exclusion criteria are fulfilled. (88).

The Mobile Stroke Unit concept was first published in 2003 and was realized in clinical practice in 2008 by Fassbender et al. at Saarland University, Germany (89). Fassbender et.al. (2003) shows that Thrombolysis in <1 hour could become possible with the mobile stroke unit which enables the starting of treatment immediately without losing time by transport to and within the hospital. Walter et.al (2018) reported a marked advantage for the Mobile Stroke Unite in decreasing treatment times (91). The second MSU was launched in Berlin, Germany in July 2011(92). The first MSU in United States

was established in Houston in May 2014 after the promising results from Homburg and Berlin (93).

The number of MSUs worldwide continues to increase every year as illustrated in Table 5.

Location	Began service	On-board personnel	Operating hours	Catchment area
Homburg, Germany	March 2011	UNK	UNK	20 km around the university hospital
Berlin, Germany	July 2011	paramedic, stroke physician, neuroradiologist	UNK	20 km around the university hospital
Fredrikstad, Norway	October 2014	neurologist, paramedic, radiology technician	07:00–11:00 daily, Monday to Sunday, randomized weeks	defined by a 75% probability of reaching the emergency sites within 16 min from base, based on calculations by the Berlin Fire Department
Houston, TX, USA	May 2014	CT technician, VN, RN, paramedic	08:00–18:00 daily, Tuesday morning to Monday evening, 50% weeks	3-mile radius
Cleveland, OH, USA	July 2014	CCN, EMT, paramedic, CT	08:00–20:00 daily	UNK
Buenos Aires, Argentina	October 2014	UNK	UNK	UNK
Denver, CO, USA	January 2016	neurologist <sup>a</sup> , CCN, technician, paramedic, EMT	UNK	UNK
Toledo, OH, USA	January 2016	VN <sup>a</sup> , critical care transport nurse, critical care transport paramedic, CT technician	24/7	defined as a 15-min drive time radius, but fire departments and EMS can also “special request” the MSU
Memphis, TN, USA	July 2016	stroke fellowship-trained doctorally prepared nurses, Advanced Neurovascular Practitioner board certified	12 h a day, 1 week on, 1 week off	10-mile radius but can be dispatched within the entire city metro area
New York, NY, USA	October 2016	neurologist, 2 paramedics, CT technician	UNK	communities surrounding NY-Presbyterian/Weill Cornell Medical Center/Columbia University Medical Center
Chicago, IL, USA	January 2017	UNK	UNK	communities surrounding Rush Oak Park Hospital that are part of Illinois Region VII
Trenton, NJ, USA	January 2017	UNK	07:00–23:00 daily	Mercer County area
Edmonton, AB, Canada	February 2017	VN <sup>a</sup> , 2 paramedics, CT technician	UNK	communities surrounding University of Alberta Hospital
Phoenix, AZ, USA	June 2017	VN and neurologists <sup>a</sup> , EMT	UNK	St. Joseph’s Hospital and Medical with 20-min response radius

CCN, critical care nurse; CT, computed tomography; EMS, emergency medical services; EMT, emergency medical technician; MSU, mobile stroke unit; RN, registered nurse; UNK, unknown; VN, vascular neurologist. <sup>a</sup> In the unit via telemedicine technology.

**Table 5: MSUs launched by June 2017(86)**



Figure 13: Current model of the Homburg mobile stroke unit. (94)



Figure 14: Stroke Unit Team. UKS. Homburg.(94).



Figure 15: Active MSU Sites with Research Programs (95).

## 2 Material and Method

### 2.1 Introduction

Although several recent trials have achieved positive results with mechanical recanalization after acute ischemic stroke with large-vessel occlusion (96–100), intravenous thrombolysis (IVT) is still the most important acute treatment for the vast majority of ischemic stroke patients (101–104). The dosage of tissue plasminogen activator (tPA) depends on the patient's weight: the approved dosage is 0.9 mg/kg to a maximum dose of 90 mg. However, uncertainties remain whether the current dosage regimen is optimal. Most reports of randomized controlled trials have not stated how patients' weights were assessed or whether weights were only estimated; only the report of the European Cooperative Acute Stroke Study II (ECASS II) states that most weights were estimated (103). More precise data were presented in the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis (SITS-ISTR) Registry: 14.6% of patients' weights were measured, whereas the remaining were estimated (105). Clinical surveys have shown that health care professionals most commonly assess a patient's weight by asking the patient or the patient's caregiver or by roughly estimating the patient's weight (106). Only a small minority of hospitals actually weigh the patient before thrombolysis is administered. Findings about whether inaccurate assessment of weight affects clinical outcomes are mostly retrospective and sometimes contradictory. However, a growing body of evidence suggests that imprecise dosage may negatively influence outcome (107–109).

No prospective trials have determined the accuracy of weights reported by the patient or estimated by the treating medical staff in the acute setting. When asked, clinicians argue that weighing the patient is either time consuming or impossible because of the

patient's immobility and the need to transfer the patient in a seated or upright position. However, these limitations can now be overcome by ground-level scales that allow the patient and the emergency medical service stretcher to be placed directly on the scale, without patient transfer. In addition, certain computed tomography (CT) tables now contain an integrated scale. After the implementation of a ground-level scale in our hospital and the integration of a scale into the CT table of our Mobile Stroke Unit (110), we prospectively compared the weights reported by the patients, those estimated by health care professional and those measured with a scale.

## **2.2 Methods**

Patients with suspected acute stroke or transient ischemic attack who were admitted to our hospital were included in this study. Written informed consent was obtained from all patients or their caregivers before the study. The study was performed in accordance with our clinical ethical guidelines and was approved by the ethics committee of the Chamber of Physicians of the Saarland.

### **2.2.1 Measuring Weight with the Ground-Level Scale:**

In our hospital, patients are admitted to the CT suite, which contains a point-of-care laboratory so that treatment delays can be reduced (111). A ground-level scale (Soehnle, Nassau, Germany; Fig. 16a) was installed in this suite so that paramedics can place the patient directly onto it upon entering the room. Thus, the patient is weighed together with the stretcher. The patient is then transferred to the CT table, and the weight of the stretcher is determined with the ground-level scale. The difference between the two results is the patient's weight. Treatment delays are avoided by measuring weight during the handover of the patient from the emergency physician to the treating neurologist.

### **2.2.2 Measuring Weight in the Mobile Stroke Unit:**

In the Mobile Stroke Unit, a scale (Soehnle, Germany; Fig. 16b) has been integrated into the CT table. Medical equipment such as monitors is removed from the stretcher during weighing. The stretcher's weight is automatically subtracted from the measured

weight. The scale in the CT table of the Mobile Stroke Unit has been successfully used for more than 50 patients with no treatment delays.

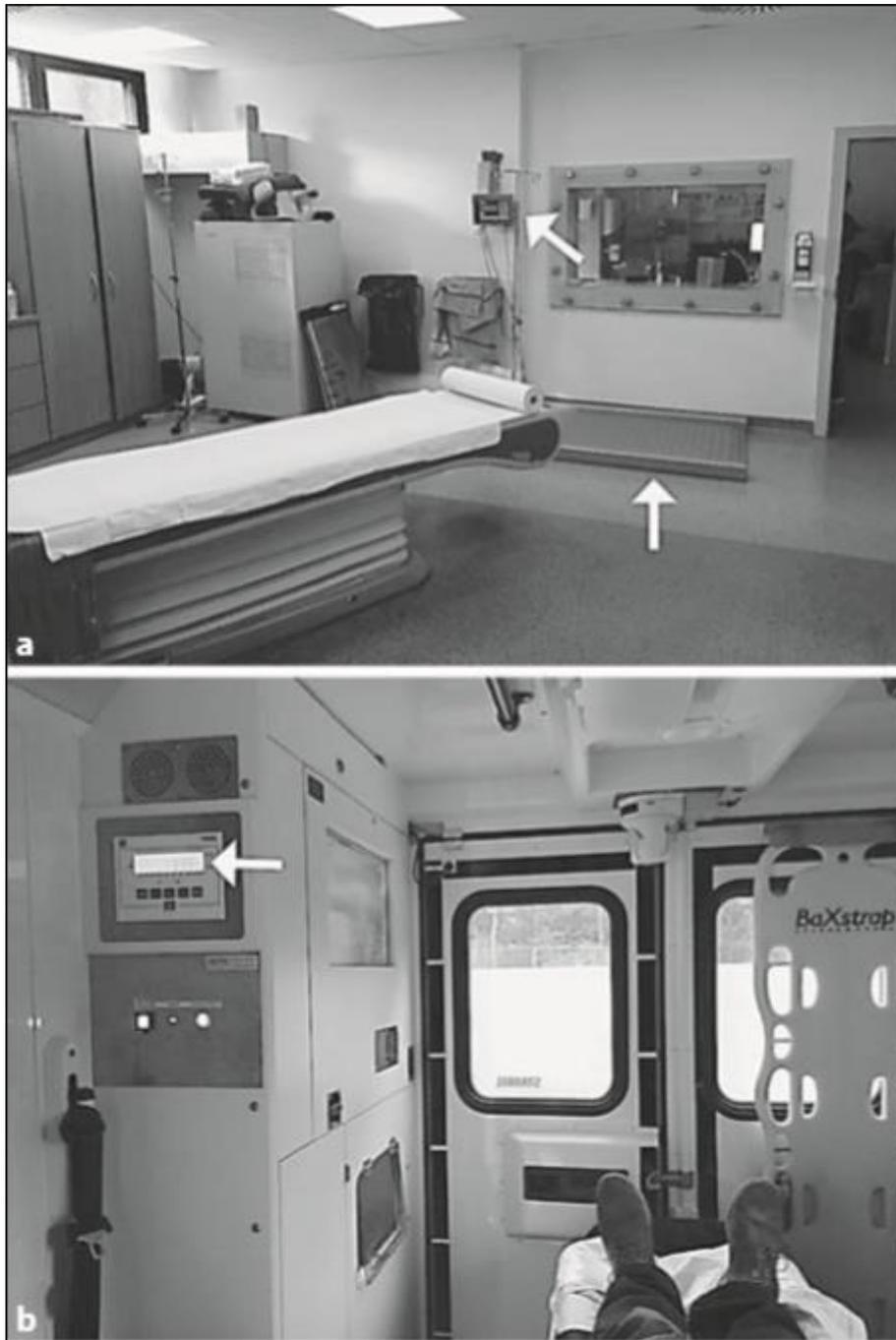


Figure 16: . A Ground-level scale and display (arrows) in the computed tomography (CT) suite of the hospital, allowing weighing of the patient during the handover procedure without additional transfer.

B. A scale integrated into the CT table of the Mobile Stroke Unit for automatic weighing of the patient. Arrow shows the display of the scale.

### **2.2.3 Comparing Reported, Estimated, and Measured Weights**

In the hospital's CT suite, an independent rater asked the patients to report their own weight. If the patient was aphasic or otherwise unable to answer, the patient's caregiver was asked to provide the weight. Next, the treating neurologist, who was unaware of either the reported or the measured weight, estimated the patient's weight. Deviations of reported and estimated weights from measured weights were analyzed statically as illustrated in Figure 19.

### **2.2.4 Statistics**

Statistical analyses were performed with IBM SPSS Statistics for Windows, version 23.0.0.2 (IBM Corporation, Armonk, NY, USA; released 2015). The difference between the absolute values of deviations of reported and estimated weights from measured weights were analyzed with *t* tests for paired variables.

Statistical significance was set at the level of  $p < 0.05$ .

### 3 Results

This study included 100 consecutive patients with suspected acute stroke (53 females, 47 males) in the period between October. 2014 and November 2015 Figure17.

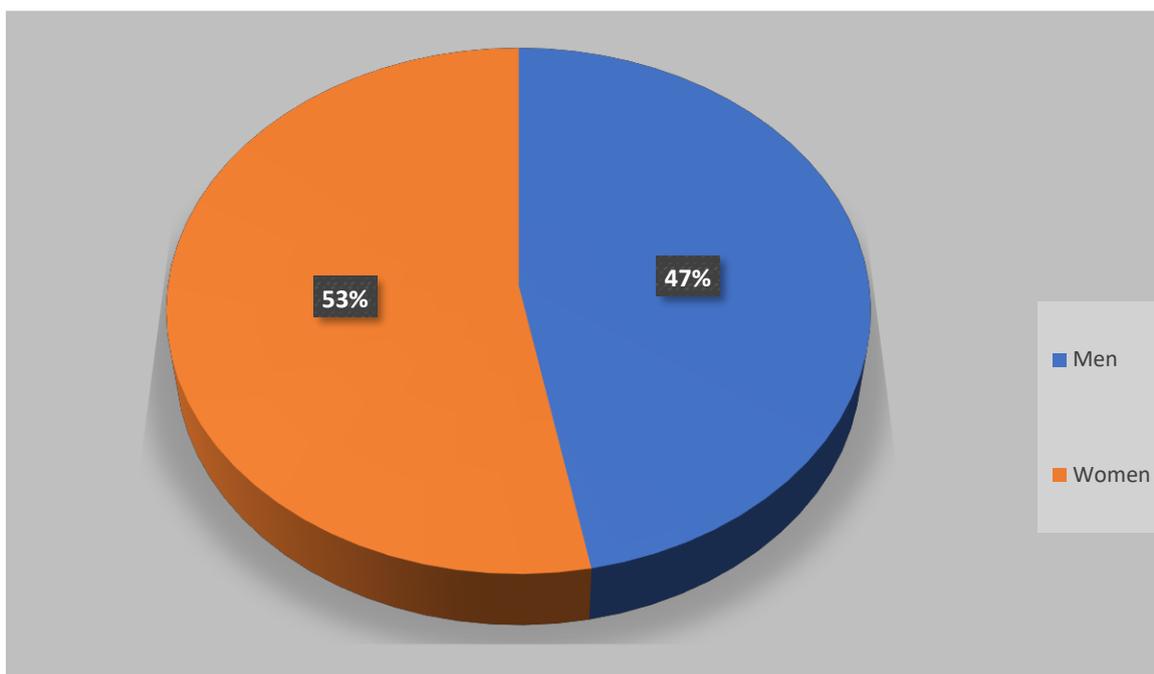
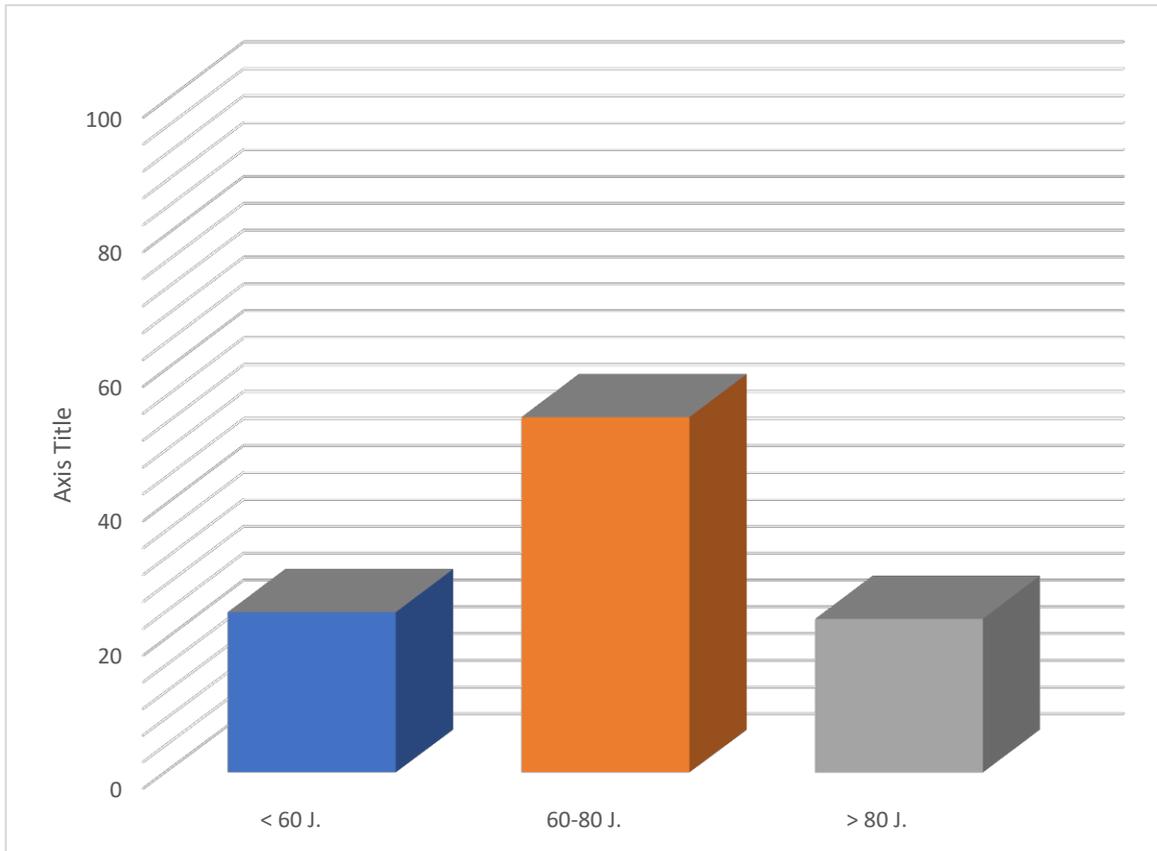


Figure 17: gender distribution

The age of patients varied from 20 years to 92 years with median age, 71.5 years.



**Figure 18: distribution**

Ten of the patients had stroke mimics, and 2 had primary intracranial hemorrhage.

IVT, mechanical recanalization, or both were necessary for 24 patients, including 3 who experienced secondary hemorrhagic transformation or bleeding into the infarct, one of these with symptomatic bleeding.

<b>Secondary intracerebral bleeding</b>	<b>frequency</b>	<b>percent</b>	<b>cumulative percent</b>
<b>Nein</b>	<b>97</b>	<b>97,0</b>	<b>97,0</b>
<b>Ja</b>	<b>3</b>	<b>3,0</b>	<b>100,0</b>
<b>total</b>	<b>100</b>	<b>100,0</b>	

**Table 6: Secondary intracerebral bleeding**

The median National Institutes of Health Stroke Scale score (NIHSS) was 4 (range, 0–40) at the time of admission Table 7.

<b>NIHSS</b>	<b>frequency</b>	<b>valid percent</b>	<b>cumulative percent</b>
0	8	8,0	8,0
1	10	10,0	18,0
2	27	27,0	45,0
3	1	1,0	46,0
4	16	16,0	62,0
5	3	3,0	64,0
6	9	9,0	74,0
8	6	6,0	80,0
10	4	4,0	84,0
12	3	3,0	87,0
14	4	4,0	91,0
16	4	4,0	95,0
17	2	2,0	97,0
18	2	2,0	99,0
40	18,0	1,0	100,0
<b>total</b>	<b>100</b>	<b>100,0</b>	

**Table 7: NIHSS score at admission**

and NIHSS was 1 (range, 0–40) at the time of discharge.

	<b>frequency</b>	<b>valid percent</b>	<b>cumulative percent</b>
0	46	46,0	46,0
1	9	9,0	55,0
2	16	16,0	71,0
3	3	16,0	74,0
4	10	10,0	84,0
5	1	1,0	85,0
6	7	7,0	92,0
8	1	1,0	93,0
10	2	2,0	95,0
12	2	2,0	97,0
14	1	1,0	98,0
16	1	1,0	99,0
100	1	1,0	100,0
total	100	100,0	

**Table 8: NIHSS score at discharge**

The median modified Rankin Scale score was 2 (range, 0–5) at the time of admission.

<b>mRS</b>	<b>frequency</b>	<b>Valid percent</b>	<b>cumulative percent</b>
0	11	11,0	11,0
1	36	36,0	47,0
2	28	28,0	75,0
3	11	11,0	86,0
4	12	12,0	98,0
5	2	2,0	100,0
Total	100	100,0	

**Table 9: Rankin score at admission**

and 1 (range, 0–6) at the time of discharge.

<b>mRS</b>	<b>frequency</b>	<b>valid percent</b>	<b>cumulative percent</b>
0	46	46,0	46,0
1	26	26,0	72,0
2	17	17,0	89,0
3	8	8,0	97,0
4	2	2,0	99,0
6	1	1,0	100,0
Total	100	100,0	

**Table 10: Rankin score at admission.**

### 3.1 Estimated and Actual Weights

Eight patients could not report their own weight because of aphasia (n = 7) 4 women and 3 men) or agitation (n = 1 woman).

The median measured weight of the patients was 76.0 kg (range, 44.0–133.4 kg).

Weighing of all 100 patients was performed during the routine handover procedure without delays.

Patients’ characteristics are displayed in Table 11.

Age, years	71.5 (20-90)
Men	47
Women	53
NIHHS score at admission	4 (0-40)
mRS score at admission	2 (0-5)
NIHHS score at discharge	1 (0-40)
mRS score at discharge	1 (0-6)
Patients unable to report weight	8
Average measured weight, kg	76.0 (44.0-133.4)
Stroke mimics	10
IVT, mechanical recanalization, or both	24
Primary ICH	2
Secondary ICH	3
Death	1
Continuous data shown as median (range), except if indicated otherwise. NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IVT, intravenous thrombolysis; ICH, intracranial hemorrhage.	

**Table 11 Patients’ characteristics (n:100).**

We have studied the reported, estimated, and measured weights in two subgroups (men and women):

The median measured weight of women was 69 kg (range 44.0- 128.8 kg) with standard deviation 14.91.

The median measured weight of men was 85.0 kg (range 58.0-133.4 kg) with standard deviation 14.59.

The median measured weight of men was 16 .0 kg more than women.

The age of patients varied from 20 years to 92 years with median age, 71.5 years and standard deviation 14.77.

The age of women varied from 20 years to 92 with median age 75 years and standard deviation 15.33.

The age of men varied from 20 years to 91 with median age 63 years and standard deviation 13.18.

The median age of women were 12 years more than the median age of men.

	Age - years	weight reported by the patient kg	weights estimated by the physician kg	Measured Weight kg
<b>available</b>	47	44	47	47
<b>unavailable</b>	0	3	0	0
<b>median</b>	63,00	85,50	84,00	85,00
<b>standard deviation</b>	13,18	13,959	13,230	14,590
<b>minimum</b>	20	60	57	54
<b>maximum</b>	91	136	140	133,4

**Table 12: women’s characteristics (age, reported, estimated, and measured weights).**

	<b>Age - years</b>	<b>weight reported by the patient kg</b>	<b>weights estimated by the physician kg</b>	<b>Measured Weight kg</b>
<b>available</b>	53	48	53	53
<b>unavailable</b>	0	5	0	0
<b>median</b>	75,00	69,50	70,00	69,00
<b>standard deviation</b>	15.332	14,643	12,890	14,9190
<b>minimum</b>	20	47	40	44,0
<b>maximum</b>	92	135	120	128,8

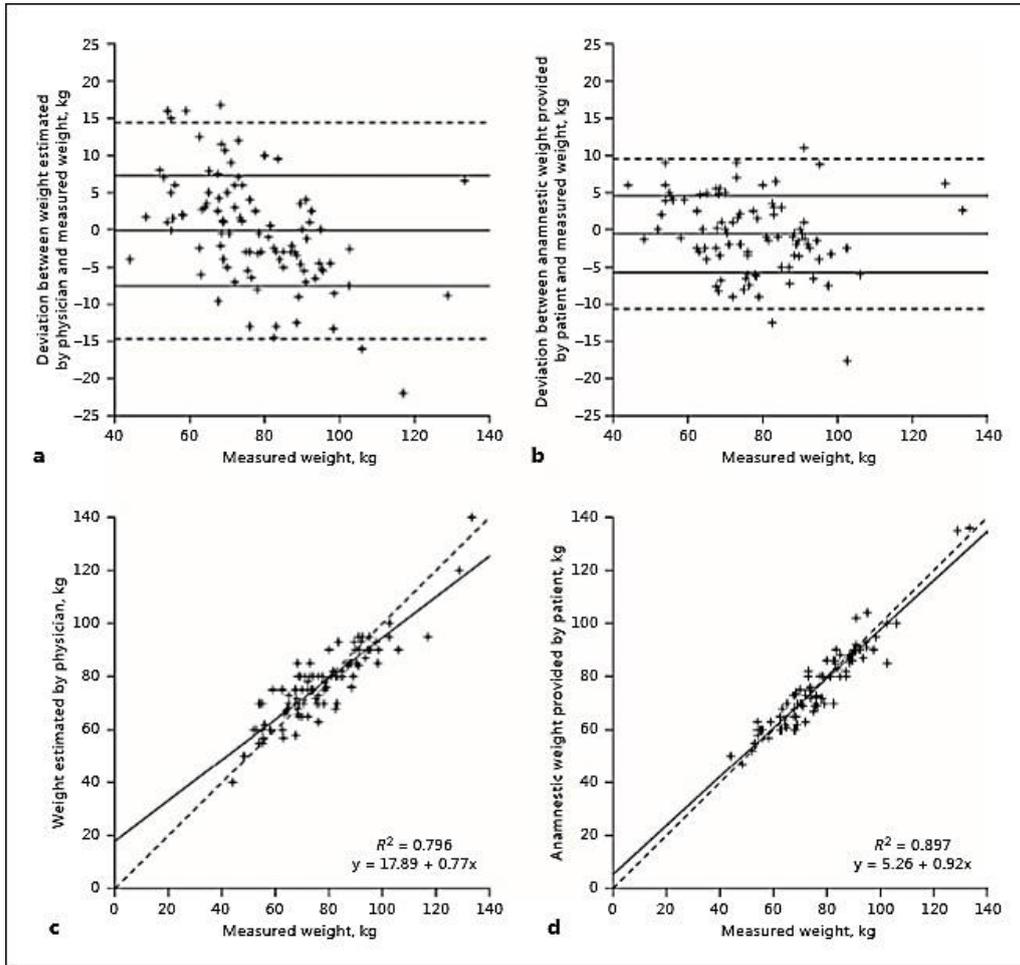
**Table 13: mens' characteristics (age, reported, estimated, and measured weights)**

	<b>Age- years</b>	<b>weight reported by the patient kg</b>	<b>weights estimated by the physician kg</b>	<b>Measured Weight kg</b>
<b>available</b>	100	92	100	100
<b>unavailable</b>	0	8	0	0
<b>median</b>	71,50	73,00	77,00	76,00
<b>standard deviation</b>	14,771	15,515	14,082	16,329
<b>minimum</b>	20	47	40	44,0
<b>maximum</b>	92	136	140	133,4

**Table 14: patients' characteristics (age,reported , estimated, and measured weights).**

## 3.2 Comparison between Estimated and Measured Weight

The weights estimated by the physician diverged from actual weights by 10% or more for 27 patients and by 20% or more for 6 patients. In absolute values, 17 estimated weights deviated from measured weights by 10 kg or more; the extremes of estimated weights were 22 kg too light and 16.8 kg too heavy (Fig. 19a). For the 92 patients for whom weights could be reported, 12 weights (13%) diverged by 10% or more from measured weights; there were no deviations of 20% or more. In absolute values, the weights of 3 patients (3.3%) deviated by 10 kg or more from measured weights; the extremes of estimated weights were 17.6 kg too light and 11 kg too heavy (Figure 19b). Reported weights differed significantly less from measured weights (mean deviation,  $4.1 \pm 3.1$  kg) than did estimated weights ( $5.7 \pm 4.4$  kg;  $p = 0.003$ , Figure 19c.d.).



**Figure 19: Modified Bland-Altman plot showing deviation of weight estimated by health care professionals from measured weight**

(a) and deviation of weight reported by the patients from measured weight. (b) The solid lines indicate means and standard deviations; the dashed lines, the 1.96-fold standard deviations. Plot shows weight estimated by the health care professionals (c) and weight reported by the patients against measured weight (d). The solid lines display simple linear regression; the dashed lines, the equality of estimated and measured weights.

The dosage of tissue plasminogen activator (tPA) depends on the reported weight by patients was incorrect in 39% of patients, and it was 13.4% more in women rather than men(45.3% women, 31.9 men) Table 15,16,17.

	Frequency	Percent
<b>Incorrect dose</b>	15	31,9
<b>Correct dose</b>	29	61,7
<b>total</b>	44	93,6
<b>unavailable</b>	3	6,4
<b>total</b>	47	100,0

**Table 15: incorrect dose according to reported weight (men n;47)**

	Frequency	Percent
<b>Incorrect dose</b>	24	45,3
<b>Correct dose</b>	24	45,3
<b>total</b>	48	90,6
<b>unavailable</b>	5	9,4
<b>total</b>	53	100

**Table 16: incorrect dose according to reported weight (women,n;53).**

	Frequency	Percent
<b>Incorrect dose</b>	39	39
<b>Correct dose</b>	53	53,0
<b>total</b>	92	92,0
<b>unavailable</b>	8	8,0
<b>total</b>	100	100

**Table 17:: incorrect dose according to reported weight (total n;100).**

## 4 Discussion

This prospective study shows that weighing acute stroke patients in the stroke treatment room or in a mobile stroke unit is feasible without treatment delays and that deviations between estimated and real weights are substantial: estimations of weight by health care professionals diverged by 10% or more from actual weight for 27% of patients.

These results are consistent with the findings of earlier studies suggesting that estimation is prone to severe errors.

Breuer et al. (107) in WAIST study found variations of as much as 42% between estimated and actual weights; the deviation was more than 10% for every third patient, it is a prospective observational monocenter study. It included 109 patient who received IVT for acute ischemic stroke (AIS) at (University Hospital Erlangen, Germany), body weight was estimated before the therapy with tPA independently by 2 physicians, 2 emergency nurses, and a neuroradiological technical assistant.

All patients after the Therapy with tPA were weighed as early as possible within 24 hours. A standard calibrated licensed scale was used when they were able to stand (Seca, Hamburg, Germany; Model 701). And the bedridden patients were weighed on a special bed scale calibrated and validated for the use for patient weighing (Seca; Model 657).

Clinical outcome was evaluated at 90 days to evaluate dosing errors.

Estimation errors rates ranged from 20.8% (patient's own estimation) up to 38.2% (treating physician) and 42.2% (emergency nurse).

29 patients received an Alteplase dosage diverging >10% from the optimal dose. Twelve were under- and 17 overdosed.

Underdosage accompanied with worse outcome in multivariate analysis.

This study proved that measuring bodyweight before Alteplase therapy remains challenging. Led to dose errors in one-third of patients and observed impact on outcome, for that standardized weighing before thrombolysis should be considered. (107).

		Incorrect Dosage		>10% Underdosage		>10% Overdosage	
		n=29	P	n=12	P	n=17	P
	Correct Dosage (n=71)						
mRS 0–1	29 (40.8%)	7 (24.1%)	0.248	2 (16.7%)	0.195	5 (29.4%)	0.385
mRS 0–2	39 (54.9%)	13 (44.8%)	0.138	3 (25%)	0.061	10 (58.8%)	0.736
siCH	2 (2.8%)	1 (3.4%)	1.000	1 (8.3%)	0.378	0 (0%)	1.000
alCH	6 (8.3%)	1 (3.3%)	0.448	0 (0%)	0.586	1 (5.9%)	1.000

**Table 18: Group Comparisons for Outcome and Safety Depending on tPA Dosage, (107).**

	mRS 2–6		mRS 3–6	
	Odds Ratio (95% CI)	<i>P</i>	Odds Ratio (95% CI)	<i>P</i>
NIHSS score on admission	1.20 (1.09–1.33)	<b>&lt;0.001</b>	1.24 (1.12–1.37)	<b>&lt;0.001</b>
Underdosage >10%	4.16 (0.78–22.23)	0.096	5.87 (1.26–27.34)	<b>0.024</b>
Age	1.03 (0.99–1.06)	0.158	1.03 (0.99–1.07)	0.160

**NIHSS on admission, underdosage >10%, and age showed a trend in univariate analysis and were entered into each model. Statistically significant *P* values (*P*<0.05) are in bold.**

**Table 19: Multivariate Analysis for Unfavorable Outcome (mRS 2–6) and Dependency/Death (mRS 3–6). (107).**

Dosing errors, n (%)	
Underdosage	16 (16%)
Overdosage	17 (17%)
Combined rates of under- and overdosage	33 (33%)
Dosing errors corrected for patients with a body weight of >100 kg, n (%)	
Underdosage	12 (12%)
Combined under- and overdosage	29 (29%)

**Table 20: Rates of Underdosage and Overdosage of >10% tPA (n=100).(107).**

Similar results were reported by Lorenz et al. (112) and Sahlas et al.(109)

Because the dosage of tPA is based on the patient’s weight, the risk of misdosing exists for a large number of patients.

Our findings of frequent incorrect estimates led us to question whether weight assessment based on estimation or on nomograms alone is still justified.

While the current dosage of tPA has been approved due to the results of the NINDS trial, there remain uncertainties regarding the ideal dosage and dosage corridor. Data from registries do not indicate a substantial risk (113). One recent study, which assessed patients' actual weights after IVT, compared a standard dose group with groups receiving overdosage or underdosage of IVT; the study found no evidence that misdosing had any effects on clinical outcome. However, these findings could be explained by the fact that this relatively small study (n = 272) may have been underpowered to address such a study question (114). On the other hand, it is implausible to assume that misdosing of a highly effective and weight-adapted drug would have no effect on clinical results, because a dose-effect relationship can be expected.

This suggestion is supported by a growing body of evidence indicating negative outcomes due to misdosing.

Sahlas et al. [109] reported that overdosed patients exhibited impaired outcome and more episodes of intracranial bleeding, and Breuer et al. [107] found that precise dosages (0.8–1.0 mg/kg) are required for optimal recanalization.

Similarly, Wahlgren et al. (108) reported that underdosage may be associated with impaired clinical outcome.

Compared with nonobese subjects, obese patients exhibit a lower rate of intracranial hemorrhage because of systematic underdosing of tPA (the ceiling dose is 90 mg). Such underdosing reduces both the beneficial and the adverse pharmacological effects of the drug (115).

Seet et al. (90) also reported about decreasing rates of intracranial hemorrhage in obese patients because of low dose of rt-PA.

A survey of 119 German stroke units found that 80.5% always or frequently estimate patients' weights. Only 4.2% of these stroke units always weigh patients, and an additional 7.6% frequently weigh them.

The most frequent answers to the question of why patients are not weighed were the following: "No opportunity to weigh patients in supine position;" "time delay;" "scale is unpractical;" "scale is too far away;" and "no scale is available." (106).

Similar results were found in the SITS-ISTR Registry, which reported that only 14.6% of patients were weighed; weights were estimated for 84.6% of patients (105).

Nomograms based on anthropometric data, such as height, waist circumference, and hip size, have been proposed for overcoming the problems of imprecise weight estimates, but such calculating devices are time-consuming. Furthermore, even with this approach, deviations of more than 10% have been reported (115).

Moreover, these surveys indicate that nomograms are almost never used in actual patient care, at least in the countries in which the survey was performed.

The recently published ENCHANTED trial, involving predominantly Asian patients compared low dose (0.6 mg/kg) versus standard dose of tPA and did not show the noninferiority of the lower dose with respect to death and disability at 90 days, but there were significantly fewer symptomatic intracranial hemorrhages (116).

Another finding of these surveys was that many hospitals do not have scales suitable for weighing acute stroke patients. This fact could be due to the potentially high costs of such scales.

The commercially available ground-level scale for hospital use and the scale integrated in the CT table cost EUR/USD 3,000 each.

However, overdosing of tPA is also costly; over time, avoiding these costs could conceivably offset the cost of a scale.

Additionally, avoiding overdosing would allow safer and more effective treatment of acute stroke patients.

As our study shows, using the ground-level scale or a scale integrated into the CT table is applicable and does not increase delays in acute stroke management; therefore, there is no reason to omit actual weighing of the thrombolysis candidate.

This study has some limitations. Although we were able to demonstrate substantial aberrations between estimated and measured weights, we could not determine whether these aberrations would lead to impaired clinical outcome. Without blinded randomization between estimated weights and measured weights it is not possible to know whether differences between them have an effect on outcome.

On the other hand, for ethical reasons, it is very unlikely that such a randomized trial could be performed once a scale has already been installed.

In conclusion, in this prospective study on weight assessment in acute stroke patients, weighing patients with acute stroke on a ground-level scale or a scale integrated into the CT table is feasible and avoids the treatment delays associated with additional transfer of the patients.

Estimates of patients' weight by health care professionals and reports of weight by the patients themselves diverge substantially from patients' measured weights.

Measuring patients' weight with a scale would avoid these deviations, improve the accuracy of tPA dosing, decrease complication and improve outcome.

# 5 Declaration of Academic Honesty

Hereby, I confirm that I have written the present dissertation independently and without any illicit assistance from third parties and using solely the aids mentioned.

I certify that the present dissertation is neither submitted nor presented to any other universities.

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