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The Relationship Between Recombinant Tissue Plasminogen Activator (rtPA) Beyond the 3 Hour Therapeutic Window and the Incidence of Intracerebral Hemorrhage in Acute Ischemic Stroke Patients

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The Relationship Between Recombinant Tissue Plasminogen Activator (rtPA) Beyond the 3 Hour Therapeutic Window and the Incidence of Intracerebral Hemorrhage in Acute Ischemic Stroke Patients

Abstract
INTRODUCTION: Thrombolytic treatment with recombinant tissue plasminogen activator (rtPA) is approved by the FDA and national institute of neurological disorders for use within 3 hours as standard therapeutic care after the onset of thrombolytic stroke. Therefore all patients who present later than 3 hours and those with an unknown time window are currently excluded from this treatment option. Thus only a small percentage of patients can benefit. It is essential to assess the safety and efficacy of tissue plasminogen activator, alteplase, when administered after the 3 hour onset for acute ischemic stroke patients to determine the increase in the incidence of intracerebral hemorrhage.

METHODS: The focus of this study is to review the current literature for the last 10 years on all studies pertaining to the safety and efficacy of tissue plasminogen activator “Alteplase” for thrombolytic stroke patients given beyond the 3 hour standard therapeutic care window. An extensive online article search via Ovid, Pubmed, and Up-to-date was performed as well as a review of articles from the years 1999-2009. Five articles were assessed along with several complimentary articles for use of thrombolysis treatment within and beyond the 3 hour time window after stroke onset.

RESULTS: A total of 5 articles; two controlled randomized trials, one prospective cohort studies, one parallel group trial, and one open label nonrandomized trial, qualified for this systematic review. Two studies indicate that Alteplase remains safe and improves clinical outcomes in patient with acute ischemic stroke. Another study concluded patient selection was more important than time of treatment for good outcome, a further study indicated that alteplase was non-significantly associated with lower infract growth and significantly associated with increased reperfusion in patients who had mismatch of diffusion weighted MRI vs. Perfusion weighted MRI, and the last study concluded that patients with large baseline of diffusion weighted MRI lesion volume who received early reperfusion appear to be at greater risk of symptomatic intracerebral hemorrhage after tPA therapy.

CONCLUSION: Based on this literature review, the use of intravenous thrombolysis alteplase improves functional outcomes at three months if given within three hours of the standard therapeutic window, however, alteplase can be given at 3 to 4.5 hours after ischemic stroke onset which will lead to moderate improvement, but it will increase the incidence of symptomatic intracerebral hemorrhage. In the last ten years several randomized trials have been published and studied on the use of thrombolysis for acute ischemic stroke beyond the three hour window, but there not enough studies to answer several questions like: which type of patients are most likely to be harmed, how accurate and precise is the benefit in these patients, what is the maximum dosage that can used in ischemic stroke patients after the three hour window without any harm to the patient? Additional randomized trials on this treatment are needed to improve the safety and efficacy of intravenous thrombolysis alteplase.

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The Relationship Between Recombinant Tissue Plasminogen Activator (rtPA) Beyond the 3 Hour Therapeutic Window and the Incidence of Intracerebral Hemorrhage in Acute Ischemic Stroke Patients

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Aklil Rostai is a native of Michigan Ann Harbor who grew up in Afghanistan until he was 18 years old. Aklil and his other members of his family decided to leave Afghanistan during the Soviet invasion and resided in America for a safer and better life. They decided to live in California and reunite with his brothers. Aklil graduated from Cerritos High School and attended San Diego State University where he received a Bachelor of Science in Biology and Psychology. He had a special interest in medicine and worked and volunteered as a medical assistant in several local hospitals and clinics to find the career of his choice. After two years, he decided to become a Physician Assistant and was accepted to five credited physician assistant programs in the United States. He was fortunate enough to be granted admission to start Pacific University Physician Assistant program in Oregon in 2006. In August 2009 he will graduate from Pacific University in Forest Grove, Oregon with a Master’s Degree in physician assistant studies. He plans to move back to California to pursue a career in Emergency Medicine/Family Medicine after graduation. He thanks God for opening doors and guiding him to the right path of life and gives special thanks and praise to his immediate family and best friends for their support to get through this program.
Abstract

INTRODUCTION: Thrombolytic treatment with recombinant tissue plasminogen activator (rtPA) is approved by the FDA and national institute of neurological disorders for use within 3 hours as standard therapeutic care after the onset of thrombolytic stroke. Therefore all patients who present later than 3 hours and those with an unknown time window are currently excluded from this treatment option. Thus only a small percentage of patients can benefit. It is essential to assess the safety and efficacy of tissue plasminogen activator, alteplase, when administered after the 3 hour onset for acute ischemic stroke patients to determine the increase in the incidence of intracerebral hemorrhage.

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KEYWORDS: Intracerebral hemorrhage, acute stroke, thrombolytic therapy, ischemic stroke, time factors, tissue plasminogen activator, magnetic resonance imaging, diffusion-weighted and perfusion-weighted imaging, hemorrhage, reperfusion therapy.
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Table of Contents

Statement of Approval ................................................................. 1
Biography ................................................................................. 2
Abstract ................................................................................. 3
Acknowledgements ................................................................. 4
Table of Contents ................................................................. 5
List of Tables ........................................................................... 6
List of Abbreviations ............................................................... 7
Introduction and Background .................................................... 8
Methods .................................................................................. 11
Results .................................................................................... 12
Review of Literature ............................................................... 13
Discussion ................................................................................ 30
Conclusion ............................................................................... 33
Tables ...................................................................................... 34
References .............................................................................. 38
List of Tables

Table I: Summary of Review of Literature Articles

Table II: Proportion of patients in the 3–4.5-h and within 3-h cohorts according to time from stroke onset to treatment.

Table III: Main and additional outcomes for patients treated between 3 h and 4.5 h compared with those treated within 3 h.
List of Abbreviations

NINDS................................. National Institute of Neurological Disorders

tPA.................................................... Tissue Plasminogen Activator

DIC........................................ Disseminated Intravascular Coagulation

DWI...................................................... Diffusion-Weighted MRI

PWI........................................... Perfusion-Weighted MRI

ICH................................................... Intracerebral Hemorrhage

NIHSSS........................................... National Institutes of Health Stroke Scale Score

SICH................................................ Symptomatic Intracerebral Hemorrhage

SITS................................................ Safe Implementation of Treatments in Stroke

ISTR................................................ International Stroke Thrombolysis Registry

mRS........................................... Modified Rankin Scale

EMEA........................................... European Medicines Evaluation Agency

TIA................................................ Transient Ischemic Attack
The Relationship Between Recombinant Tissue Plasminogen Activator (rtPA) Beyond 3 Hours Therapeutic Window And The Incidence of Intracerebral Hemorrhage In Acute Ischemic Stroke Patients.

**Introduction**

A stroke is characterized by the sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function. An ischemic stroke is caused by a block in a blood vessel that stops the flow of blood and deprives the surrounding brain tissue of oxygen. In the absence of oxygen, the brain cells in the immediate area begin to die and release toxic chemicals that damage brain tissue in the surrounding area. A stroke can occur when the blood supply to a part of the brain is interrupted or severely reduced, depriving brain tissue of oxygen and within a few minutes, brain cells begin to die. A stroke is a medical emergency, and a rapid treatment is crucial. If a stroke is treated early it can minimize damage to the brain and potential stroke complications. There are two types of stroke Ischemic stroke and Hemorrhagic stroke.

**Ischemic stroke:**

Ischemic stroke is the most common occurring for about 80 percent of all strokes. They occur when the arteries to the brain are narrowed or blocked, causing severely reduced blood flow or ischemia. The most common types of ischemic strokes are:
1. **Thrombotic stroke**- This type of stroke occurs when a blood clot (thrombus) forms in one of the arteries that supply blood to the brain. A blood clot usually forms in areas damaged by *atherosclerosis* — a disease in which the arteries are clogged by fatty deposits or plaques.¹

2. **Embolic stroke**- An embolic stroke occurs when a blood clot or other particle forms in a blood vessel usually from the heart, or from the lower extremities and travels the bloodstream to block the smaller arteries in the brain. This type of blood clot is called an *embolus*. It is mostly caused by an irregular heart beat which leads to poor blood perfusion and allows the clot to form.¹

**Hemorrhagic stroke:**

A hemorrhagic stroke occurs when a blood vessel in the brain leaks or ruptures. This can result from different conditions that have an effect on the blood vessels, including *uncontrolled high blood pressure* or *hypertension* and weak spots in the blood vessel walls known as aneurysms. There are two main types of hemorrhagic stroke¹:

**Intracerebral hemorrhage**- This type of stroke is occurs when a blood vessel in the brain bursts and spills blood into the surrounding tissue, and damaging the cells. High blood pressure is the most common cause of hemorrhagic stroke. Constant high blood pressure can cause these small arteries in the brain to become delicate and susceptible to rupture.

**Subarachnoid hemorrhage**- In this type of stroke bleeding starts mainly in the large artery and spills blood into the area between the subarachnoid space and skull. It is often caused by a sudden and severe "thunderclap" *headache* or by the rupture of an aneurysm, which may be due to increased age or genetically inherited. The management and
treatment of patients who have an ischemic stroke involves several critical steps like: Ensure the medical stability of the patient, reverse any conditions that contribute to the symptoms of stroke, screen for potential contraindications to thrombolysis and timely restore blood flow using thrombolytic.

Treatment with medications for ischemic stroke involves dissolving the clots with drugs which must be administered within 3 hours of the onset of the symptoms. These treatments not only improve the chances of survival, but also reduce complications resulting from the stroke.¹

**Aspirin**- Aspirin is the best-proven immediate treatment after a stroke to reduce the likelihood of having another stroke. In the event of a hemorrhagic stroke, taking aspirin could worsen the bleeding. Other blood-thinning drugs, such as *warfarin* (*Coumadin*) and heparin also may be given, but they aren't as commonly used as aspirin.¹

**Tissue plasminogen activator**- Some people who are having a stroke can benefit from an injection of tissue plasminogen activator “rtPA”. TPA is a potent clot dissolving drug that helps some people who have had stroke to recover more fully.¹ However, the drug can only be given to patients within a three-hour window of the stroke occurring, and it can only be given in situations in which doctors are certain that giving TPA will not worsen the bleeding in the brain. TPA is contraindicated in people who are having a hemorrhagic stroke. Intravenous thrombolysis with Alteplase is the only approved treatment for acute ischemic stroke. It is currently approved by the FDA and by the European medicine evaluation committee in for acute ischemic stroke. The use of tissue plasminogen activator is approved up to 3 hours after the onset of ischemic stroke symptoms, but despite the overall positive outcome, a significant risk of thrombolysis
related intracranial hemorrhage still remains. The efficacy and safety when administered more than 3 hours after the onset of symptoms has not been established. The objective of this research paper is to determine whether a patient who presents with ischemic stroke after 3 hours or those with an unknown time window, can still benefit from intravenous thrombolysis Alteplase without increase in the risk of intracerebral hemorrhage.21

**Materials and Methods**

A comprehensive literature search was compiled using the keywords: Intracerebral hemorrhage, acute stroke, thrombolytic therapy, ischemic stroke, time factors, tissue plasminogen activator, magnetic resonance imaging, diffusion-weighted and perfusion-weighted imaging, hemorrhage, and perfusion therapy. Literature from 1999 to the present was reviewed and analyzed for importance in answering the clinical question. The focus of study was to determine if thrombolytic therapy after three hours would increase the risk of early symptomatic intracerebral hemorrhage, death and other adverse affects. Each article was reviewed and graded on the following criteria: randomization, type of studies, sample size, adverse affects, reperfusion-weighted MRI, diffusion-weighted MRI, magnetic resonance imaging, control group, age, and duration of treatment and time window. These results were then compiled and analyzed. The inclusion criteria were all pertinent English language articles or data, published after 1999 that aided in explaining the effects of the intravenous thrombolytic, alteplase, beyond the 3 hour window for acute ischemic stroke patients. Exclusion criteria included articles published before 1999, review studies, observational studies of thrombolytics, articles that used Human Tissue Urokinase type activator instead of rtPA. Also excluded were patient who had severe intracerebral hemorrhages or early ischemic changes in
more than one third of the middle cerebral artery on baseline CT, and patients older than 80 years of age.

**Results**

A total of 5 articles; two controlled randomized trials, one prospective cohort study, one parallel group trial and one open label nonrandomized trial, qualified for this systematic review. Two studies indicate that alteplase remains safe and improves clinical outcomes in patient with acute ischemic stroke. Another study concluded patient selection was more important than time of treatment for a good outcome, a further study indicated that alteplase was non-significantly associated with lower infarct growth and significantly associated with increased reperfusion in patients who had a mismatch of diffusion weighted MRI versus perfusion weighted MRI, and the last study concluded that patients with a large baseline of diffusion weighted MRI lesion volume who received early reperfusion, appeared to be at greater risk of symptomatic intracerebral hemorrhage after tPA therapy.

Hacke, and Kaste examined the current efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke because its efficacy and safety when administered more than 3 hours after the onset of symptoms have not been established. The Study selection was prioritized and randomly assigned patients with acute ischemic stroke in a 1:1 double blinded fashion to receive treatment with intravenous alteplase 0.9 mg per Kg of body weight or with placebo. Patients were accepted into the study if they were 18 to 80 years of age, had a diagnosis of acute ischemic stroke and were able to receive the study drug within 3 to 4 hours after the onset of symptoms. The study enrolled 821 patients of which 418 was randomly assigned to
treatment with alteplase, thirteen people were lost due to lack of follow-up, and among the 403 patients that were assigned to receive placebo, ten people were lost due to lack of follow-up. The median for the administration of the alteplase was 3 hours and 59 minutes. A total of 771 patients were evaluated by the means of CT and fifty patients by the means of MRI at baseline. Alteplase and matched placebo were reconstituted from a lyophilized powder in sterile water for injection. Of the total dose only 10% was administered as a bolus, and the remainder was given by continuous intravenous infusion over a period of 60 minutes. A cerebral computed tomographic (CT) scan was required before randomization to exclude patients who had an intracranial hemorrhage or major ischemic infraction.

The primary end point disability at ninety days, dichotomized as a favorable outcome a score of (0-1) on the modified Rankin scale which has a range of zero to six, with zero indicating no symptoms at all and six indicating death. The secondary end point was global outcome analysis of four neurologic and disability scores combined. The safety end points included death, symptomatic intracranial hemorrhage or any other adverse events. For patients that were lost from the study the worst possible outcome for the primary end point were inputted. Those patients that were excluded from the study had a history of stroke and diabetes, treatment with oral anticoagulant within 24 hours, broken medication code, treatment with a prohibited medication, diagnosis of ischemic stroke, or had not signed an informed consent or had withdrawn consent. The results of the study showed, that more patients had a favorable outcome with Alteplase than with the placebo (52.4% vs. 45.2%; with odds ratio of 1.34 at 95% confidence interval [CI], 1.02 to 1.76; P=0.04). In the global analysis the outcome was also improved with the
alteplase group compared to the placebo group; with an odds ratio of (1.28; 95\% CI, 1.00 to 1.65; P<0.05). The incidence of intracranial hemorrhage was much higher with the alteplase group compared to the placebo group, (27.0\% vs. 17.6\%; P= 0.001) and for symptomatic intracranial hemorrhage, 2.4\% vs. 0.2\%; P=0.008). There was not a significant difference in the mortality rate between the alteplase group and the placebo group; (7.7\% and 8.4\% respectively; P=0.68).³

More specifically in this randomized, placebo controlled study, a total of 66 patients died, 418 patients in the alteplase group 32 patients (7.7\%) and 34 patients out of 403 patients in the placebo group (8.4\%). Also there were more cases of intracranial hemorrhage in the alteplase group than placebo group. The incidence of symptomatic intracranial hemorrhage with alteplase was less than three cases per 100 patients (10 of 418 patients [2.4\%]), but the incidence was significantly higher than the incidence with placebo (1 of 403 patients [0.35]; odds ratio, 9.85; 95\% CI, 1.26 to 77.32; P=0.008). All symptomatic intracranial hemorrhages occurred within the first 22 to 36 hours after initiation of treatment. The rate of symptomatic edema did not differ significantly between the study groups; 6.9\% in the alteplase group and 7.2\% in the placebo group.³

Hacke, sited the 1995 study by the National Institute of Neurological Disorders and Stroke (NINDS) which reported that patients with acute ischemic stroke who received alteplase (0.9 mg per Kilogram of body weight) within 3 hours after the onset of symptoms were at least 30\% more likely to have minimal or no disability at three months than those who received placebo. Also the subsequent analysis of the NINDS study and combined analysis of data from six randomized trials which investigated thrombolysis treatment for ischemic stroke in a total of 2775 patients showed a clear association
between treatment efficacy and the interval between the onset of symptoms and the administration of the thrombolytic agent. The analysis suggested that the longer time window, as compared with the shorter time window was not associated with higher rates of symptomatic intracranial hemorrhage or death. The overall rate of symptomatic intracranial hemorrhage in this study was increased with the alteplase group compared to the placebo group, but there was no significant difference in the mortality rate between the alteplase group and the placebo group.

In this study the intravenous alteplase given 3 to 4.5 hours after the onset of ischemic stroke symptoms was associated with a significant improvement in the clinical outcome, with higher rate of symptomatic intracranial hemorrhage than that reported previously among patients treated within 3 hours. Although the finding in this study suggests that treatment with alteplase may be effective in patients who present 3 to 4.5 hours after the onset of ischemic stroke symptoms, patients should be treated with alteplase as early as possible to maximize the benefit.

Davis, et al all experimented whether alteplase given 3-6 hour after the onset of stroke promotes reperfusion and attenuates infract growth in patients who have a mismatch in perfusion-weighted MRI (PWI) and diffusion-weighted MRI (DWI). The aim was to establish the effect of intravenous alteplase on the growth of lesions, reperfusion, and clinical outcomes in penumbral patients 3-6 hours after stroke onset. This study was a prospective placebo-controlled randomized trial that was done between 2001 and 2007 in fifteen centers in Australia, New Zealand, Belgium, and the U.K, and included 101 patients with acute hemispheric ischemic stroke. Patients from age eighteen years or older had a National Institute of Health Stroke Scale Score (NIHSS) of more
than 4, and had a premorbid modified Rankin score (mRS) of 2 or less was included. The study randomly assigned fifty two patients to the alteplase group and forty nine patients to the placebo group. PWI and DWI were done on each patient within 3-5 days after therapy, with T2-weighted MRI at around day 90. A baseline screening with a non-contrast CT scan was done with both groups to exclude acute hemorrhage and major early ischemic changes (defined as ischemia of more than one-third of the middle cerebral artery).4

Patients were treated with the next sequentially numbered treatment pack, which contained either alteplase (0.9 mg/Kg up to maximum of 900 mg, 10% was administered as bolus and the remainder over one hour) or the placebo in a double-blinded design. The primary endpoint was infarct growth between baselines DWI at day 90 in mismatch patients. And major secondary endpoints were reperfusion, good neurological outcome, and good functional outcome.4 This randomized trial study collected 3908 patients, who were screened initially with MRI, and 1224 of these patients were screened within 6 hours and fifty two were randomly assigned to the alteplase group and forty nine patients to the placebo group. The principle reason for the exclusion of 2684 of the patients was that they were not screened within six hours, 355 patients had hemorrhage on screening CT, 245 had indication for alteplase treatment within three hour, 196 had NIHSS score of < 4, 111 had rapidly resolving symptoms, eighty five declined informed consent, eighty seven had other diagnosis, eighty six had morbidity, in thirty five patients their MRI was not done within six hour, and twenty four had major ischemic change.4

The baseline variables of patients with mismatch of PWI and DWI were similar between alteplase and the placebo group. Of the forty two patients with mismatch who
received alteplase, all had assessment of clinical outcome and thirty seven had a valid imaging outcome, and all forty three patients who had mismatch and received placebo, had clinical and valid imaging outcomes. Out of eighty seven total patients with adequate baseline MRA scans, 62% had arterial obstruction, the ratio of geometric means between the alteplase and placebo group was not significant, (0.69 at 95% CI, P= 0.239). Infract growth was significantly lower in mismatch patients who received alteplase than in those who received placebo. Both the incidence of reperfusion and the median percentage of reperfusion were significantly higher in patients with mismatch who received alteplase than in the placebo group. Reperfusion was significantly associated with lower geometric mean infract growth, good neurological outcome, and good functional outcome for all patients and mismatch patients. The incidence of intracranial hemorrhage was 7.7% (95% CI 2.1-18.5) with alteplase and 0% with placebo group. The mortality rate did not differ significantly when the alteplase group was compared to the placebo group for all patients.4

This study concludes that the primary outcome, lower infract growth with alteplase in mismatch patients, was negative when analyzed by the ratio of geometric means. However, other growth measures, the relative growth and proportion of patients with no infract growth supported the hypothesis of attenuated infract growth with alteplase beyond 3 hours. Treatment with intravenous alteplase within 3-6 hours of stroke onset did not result in significantly lower infract growth across all measures and significant increase in reperfusion. Reperfusion was increased by alteplase 3-6 hours after the onset of ischemic stroke and was strongly associated with infract growth attenuation, good neurological outcome and good functional outcome. In this study the sample size
was too small to assess the effects of alteplase on clinical outcome in patients who had a mismatch of DWI and PWI. The study also did not plan to use mismatch in the selection of patients, because rapid online detection of mismatch was not feasible and they were eager to include a proportion of patients without mismatch for an exploratory analysis.

The strength of the study included the effective randomization, good matching of key baseline prognostic determinants, and inter-observer agreement of imaging parameters. The weakness of the study lay in low power to test some hypotheses like primary endpoint of growth attenuation. This study provides further evidence that the time window for thrombolysis treatment might be extended beyond 3 hours in some patients. Alteplase was non-significantly associated with lower infract growth and significantly associated with increased reperfusion in patients who had mismatch, and because reperfusion was associated with improved clinical outcomes, a phase III trial beyond the 3 hours after treatment with clinical endpoints, needs to be further studied.

Lansberg, enrolled a total of seventy-four patients prospectively in an open-labeled study of intravenous tPA administered between 3 and 6 hours after symptom onset and an MRI was obtained before 3 to 6 hours after tPA administration. Patients were eligible if they had a clinical syndrome consistent with stroke, a National Institute of Health Stroke Scale Score (NIHSSS) of ≥ 5 and no evidence of acute hemorrhage or clearly identifiable hypodensity involving the 1/3 middle cerebral artery distribution on pretreatment CT scan. Enrolled patients also underwent an MRI, including diffusion-weighted MRI- (DWI) and perfusion-weighted MRI (PWI), before 3 and 6 hours after tPA administration of (0.9 mg/kg). Patients who developed worsening of 2 or more points
on the NIHSS underwent an urgent CT or MRI, and, if any degree of brain hemorrhage was detected on these patients, an independent Data Safety and Monitoring Board (DSMB) reviewed the clinical and imaging data. The DSMB classified symptomatic hemorrhage as either “minor” if it was associated with 2 to 3 points of worsening on the NIHSS within 36 hours of tPA administration or “major” if it was associated with 4 or more points of worsening within 36 hours of tPA administration.

Baseline variables that were obtained for each patient included: age, gender, history of cardiac disease, smoking, diabetes, stroke/TIA, hypertension, hyperlipidemia, serum glucose, and platelet count, systolic and diastolic at admission, NIHSSS, DWI lesion volume and PWI lesion volume. Symptomatic intracerebral hemorrhage occurred in seven out of seventy four patients, four major and three minor and three of the four major SICH patients died. Of the three patients with minor SICH only one died. The NIHSSS, DWI lesion volume, PWI lesion volume, and reperfusion status were associated with an increased risk of SICH (P < 0.05). In addition, the rate of reperfusion between the baseline and 3 to 6 hour follow-up MRI scan for early reperfusion was greater in patients with SICH than in those without.

In multivariate analysis, DWI lesion volume was the single independent baseline predictor of SICH (odds ratio 1.42; 95% CI 1.13 to 1.78 per 10 ml increase in DWI lesion volume), and, when early reperfusion status was included in the predictive model, the interaction between DWI lesion volume and reperfusion status was the only independent predictor of SICH (odds ratio 1.77; 95% CI 1.25 to 2.50 per 10 ml increase in DWI lesion volume).
Patients with major SICH typically had baseline DWI volume > 90 ml and, both major and minor hemorrhages occurred almost exclusively in patients who experienced early reperfusion. Only one of the baseline CT scans of patients with SICH showed evidence of clearly identifiable hypodensity involving more than 1/3 of the middle cerebral artery. This patient had a major hemorrhage 4 hours after tPA treatment and died the same day.5

In this study patients with large baseline DWI lesion volumes who achieve early reperfusion appear to be at greatest risk of symptomatic intracerebral hemorrhage after tPA therapy. There was a significant interaction between DWI volume and early reperfusion, which indicates a synergistic effect, on the risk of SICH between DWI lesion volume and early reperfusion.

The finding in this study also states, that DWI volume is an independent predictor of SICH and is in accord with previous reports that have shown that the extent of early infract signs on CT is a predictor of SICH because both large DWI lesions and widespread CT hypodensity are markers of the severe cerebral ischemia. Because the previous study DEFUSE, excluded patients with hypodensity involving more than 1/3 of the middle cerebral artery on the CT, this study was unable to assess the influence of major early infract signs on CT, in this study. Little is known about the relationship between reperfusion and the development of SICH in patients that are treated with intravenous tPA. It has been postulated that, reperfusion related damage to the ischemic microvasculature may contribute to the risk of symptomatic intracerebral hemorrhage. The finding in this study supports this view as, reperfusion, particularly in patients with
large baseline DWI lesion volumes, was associated with increased risk of symptomatic intracerebral hemorrhage.² ⁵

Kohrmann performed a nonrandomized cohort study, where he assessed the clinical outcomes and incidence of symptomatic intracerebral hemorrhage (ICH) in 400 consecutive patients treated with intravenous rtPA from March of 1998 to October of 2005. Data were prospectively obtained and entered into a local database, including information about age, gender, time of onset of symptoms, time of treatment, modified Rankin scale (mRS) score at 90 days, baseline Institutes of Health Stroke Scale Score (NIHSSS) at day 1 and 7, imaging data, medication use and relevant disease.⁶ All the analysis was done retrospectively using the collected data. At the institution, an algorithm was used whereby patients eligible for thrombolysis within 3 hours, and, if time of onset is unclear, MRI was used.

Patients in this study received both MRI and CT in a random order before treatment was initiated. Patients were also selected on the basis of MRI findings and treated at the institution only if a PWI-DWI mismatch was present. No upper limit of age or stroke severity was applied, only patients with an apparent DWI lesion exceeding 50% of the middle cerebral artery were excluded from thrombolysis treatment. A total of 18 patients were excluded from the analysis who received rtPA beyond 3 hour on the basis of CT findings. The remaining 382 patients were divided into three groups: CT-based treatment within three hours (n=209); MRI-based treatment within 3 hour (n=103); and MRI-based treatment beyond the three hour window (n=70).

Baseline stroke severity was very similar in all three subgroups (median NIHSSS=13). Patients in group three (MRI > 3 h) had a similar 90 day outcome to those
in the other two groups (48% were independent in the CT < 3 h group, 51% in the MRI < 3 h group, and 56% in group three), but without an increased risk for symptomatic ICH (9%, 1%, 6%) or mortality (21%, 13%, 11%). MRI-selected patients overall, had a significantly lower risk than CT-selected patients for symptomatic ICH (3% vs. 9%; P=0.013) and mortality (12% vs. 21%; P=0.021).

Time to treatment did not affect outcomes. Also, incidence of ICH was significantly lower in patients treated according to MRI findings, than in those treated according to CT finding. In multivariate regression analysis this favorable response for MRI-based treatment was shown to be independent of the other factors that were examined. Also, increasing age and the severity of stroke were strong predictors for a worse outcome in all analyses. Symptomatic ICH, strongly predicted worse functional recovery. 75% of patients with symptomatic ICH died within the first 90 days and overall, patients who received treatment based on MRI findings had a significantly lower mortality rate than those treated on the basis of CT findings.  

The data from this study concludes that beyond three hours and maybe even within three hours, patient selection is more important than time in treatment for a good outcome. Furthermore, MRI-based thrombolysis, in spite of the time window, shows an improved safety profile while being at least as effective as standard CT-based treatment within 3 hours.  

Wahlgren, experimented outcomes in patients treated between 3 hour and 4.5 hour versus those patients treated within 3 hours, who were recorded in the Safe Implementation of Treatments in Stroke (SITS), through a prospective internet-based audit of the International Stroke Thrombolysis Registry (ISTR). This study included
patients presenting with ischemic stroke that were given intravenous alteplase between 3 hours and 4.5 hours after symptom onset and registered in SITS-ISTR. As a comparison, the study considered patients treated within 3 hours and registered in SITS-ISTR.

Patients received a full dose of alteplase (0.9 mg/kg with an upper limit of 90 mg) with continuous infusion over 60 minutes, with 10% of the total dose administered as a bolus. The investigators in the study documented baseline and demographic characteristics, stroke severity measured by score in National Institute of Health stroke scale (NIHSS), onset of treatment time, risk factors, medication history, admission to the hospital and follow up imaging scans. Outcome measures were symptomatic intracerebral hemorrhage within 24 hour associated with the National Institute of Health Stroke Scale [NIHSS] > 4 points deterioration and mortality (modified Rankin scale of 0-2) at 3 months. The study included data for 664 patients with alteplase treatment started between three hours and 4.5 hours after ischemic stroke onset and for 11865 patients treated within three hours. In the 3-4.5 hour cohort, treatment was started at a median of 55 minutes later after symptom onset, median age was 3 years younger, and stroke severity was one point lower as measured by the NIHSS score than in the 3 hour cohort (195 min) vs. (140 mint), P<0.0001. The median age was three years younger (65 years vs. 68 years), P< 0.0001. The stroke severity was lower (NIHSS score 11 vs. 12), P<0.0001 than in the 3 hour cohort. There were no significant differences between the 3-4.5 hour cohort and within 3 hour cohort for any outcome of symptomatic intracerebral hemorrhage (2.2% vs. 1.6%), odds ratio 1.18 at 95% CI, P=0.24. mortality (12.7% vs. 12.2%) odds ratio 1.02, P=0.72. Also at three months the study noted no significant
difference between the cohorts, in mortality rates or functional independence (modified Rankin scale score 0-2). The two cohorts did not differ significantly in any primary cause of death. The study recorded intracerebral hemorrhage as a primary cause of death for 1.2% of patients treated between 3 hour and 4.5 hour and 1.1% for those treated within 3 hour, P=0.92. Death from a cerebral infract was the most common cause of death, occurring in 5.0% of patients in the 3-4.5 hour cohort compared to 4.4% in the patients in the within 3 hour cohort.² ⁷

The results from in this study showed that the rates of symptomatic intracerebral hemorrhage, mortality and independence at 3 months follow-up routine clinical practice are similar between patients who were treated within 3-4.5 hour and for those patients treated within 3 hour after ischemic stroke onset. This suggests that alteplase remains safe when given at 3-4.5 hour after ischemic stroke, offering the opportunity for patients who cannot be treated within the standard 3 hour therapeutic timeframe.

**Discussion**

The primary goal of this systematic review was to identify evidence from the current medical literature on the use of thrombolytic therapy for acute ischemic stroke patients. Thrombolytic therapy is one of the most promising treatments for acute ischemic stroke. It can reduce disability after stroke, but can cause serious bleeding. The majority of the stroke that occurs is due to blockage of an artery in the brain by clot. Treatment with thrombolytic drugs like alteplase can restore blood flow before major brain damage occurs. However thrombolytic drugs can cause serious bleeding in the brain and can be fatal. Intravenous thrombolysis tissue plasminogen activator, alteplase, is currently the only therapy approved by the FDA and the European Union for acute
ischemic stroke. Thrombolytic therapy has now been evaluated in several randomized and cohort trials in acute ischemic strokes. The thrombolytic drug alteplase (rtPA) has been proven and licensed for use within three hours of stroke in the United States, Canada and recently in most European countries, however only a small percent of patients can benefit within the three hour therapeutic window.

Hacke conducted a randomized placebo-controlled study to test the safety and efficacy of alteplase between 3 and 4.5 hours after the onset of a stroke and he concluded that patients in his study benefited from the treatment with intravenous alteplase. The benefit of intravenous alteplase beyond the three hour treatment window was also discussed in 2008 by the ECASS III trial, which concluded that intravenous alteplase is still beneficial when given up to 4.5 hours after stroke onset, and more patients had favorable outcome with alteplase than placebo, (odds ratio 1.34 at 95% CI 1.02-1.76). In this study the rates of symptomatic intracerebral hemorrhage between the two groups was significant, the incidence of symptomatic intracerebral hemorrhage was higher in the alteplase group than placebo group. The mortality rate between the alteplase and placebo group was not significant, but symptomatic intracranial hemorrhage was significantly higher in the alteplase group than the placebo group. 1,4,7

The SITS-ISTR observational study compared the outcome in patients treated with alteplase for acute ischemic stroke compared to the patients treated between three hours and 4.5 hours and patients treated within three hours had similar rates of independence, symptomatic intracerebral hemorrhage and mortality rate. In contrast to these recent studies, earlier randomized trials of intravenous thrombolysis did not show a clear benefit for patients treated more than three hours after the onset of ischemic stroke; however,
these earlier trials had the treatment time window of up to six hours and only a small numbers, of patients was treated between three and 4.5 hours. Data from the SITS-ISTR centers show that only a small proportion of all treated patients receive thrombolysis within 3-4.5 hours timeframe; for most patients seventy four percent, treatment started within three hours and the remaining twenty two percent of patients in the registry failed to satisfy other selection criteria of the present labeled use of alteplase. No data are available within SITS-ISTR for the reasons for treatment outside the three hours limit. One reason could be that clinicians decide not to withhold treatment if a patient has been prepared and informed about thrombolysis within three hours, but more than three hours can elapse because of unforeseeable delays in the pre evaluation phase before treatment can be started. Another reason might be that some clinicians base their decision to begin treatment up to 4.5 hours after stroke onset on the significant benefit reported in the meta-analysis of all available data. One of the limitations of this cohort study and analysis for the outcome data in the 3-4.5 hours is the observational design. In large, multinational, multicenter registry studies aimed at collecting data indicative of routine clinical practice, perceptual and technical differences between centers are possibility that could have affected the assessment of intracerebral hemorrhage. Also the potential bias of patients’ selection for treatment beyond the three hours time frame is another consideration.

According to Wahlgren, Hack, and Kohrmann the results showed, the odds of favorable outcome significantly decreased as the interval from stroke onset to start of alteplase treatment increased. The results from this study concludes that the earlier the intravenous alteplase treatment is initiated after the onset of ischemic stroke, the more beneficial the outcome. Also the study found that the treatment time window of
intravenous alteplase for ischemic stroke patients can be extended to 4.5 or even five hours, but the odds ratio will decrease when treatment with alteplase is used beyond the three hour window. The risk of symptomatic intracerebral hemorrhage was higher in the alteplase group compared to the placebo group.

According to Davis, a placebo-controlled randomized trial compared whether alteplase given 3-6 hours after stroke onset promotes reperfusion and attenuates infarct growth in stroke patients, and the study found no significant benefit with lower infarct growth on the primary MRI outcome measures. The study suggested that recanalization was more common after tPA and was associated with less infarct growth and better clinical outcomes. Another study that was done in 2007 was a multicenter German study that used MRI screening criteria to select patients with acute ischemic stroke for the use of intravenous tPA treatment. The study was not randomized, but the study made comparisons with pooled data from other studies; NINDS, ATLANTIS, and ECASS II trials that experimented the use of tPA or placebo within 6 hours. The results from the alteplase group were (odds ratio 1.65, at 95% CI 1.0-2.75) and the results from the placebo group were (odds ratio 1.78 at 95% CI 1.07-2.96) from three hours to six hours, and there was no agreement regarding the best technique to measure ischemic penumbra on MRI. The results from the DEFUSE trial also suggested that reperfusion with intravenous tPA from three to six hour after stroke onset will result in a more favorable clinical outcomes in patients who have a baseline diffusion-perfusion mismatch than those patients who have no mismatch.

This review confirms that the use of thrombolytic therapy can reduce the risk of disability and mortality and that the treatment time window can be extended to beyond
the three hour window, but results indicate that the odds of favorable outcome will decrease as the interval from the stroke onset to start tPA treatment increase. However, there is not currently enough evidence to prove the safety and efficacy of intravenous thrombolysis in acute ischemic stroke patients beyond three hours.

**Conclusion**

Based on this literature review, the use if intravenous thrombolysis alteplase improves functional outcome at three months if given within three hours of the standard therapeutic window. However, it would appear to be relatively safe to administer alteplase up to 4.5 hours after the onset of acute ischemic stroke which would lead to an overall improvement in three month outcome, but may increase the incidence of symptomatic intracerebral hemorrhage. Despite the small percentage increase in the risk, the use of alteplase may be justified. In the last ten years several randomized trials have been published and studied on the use of thrombolysis for acute ischemic stroke beyond the three hour window, but there are not enough studies to answer several questions like: which type of patients are most likely to be harmed, how accurate and precise is the benefit in these patients, what is the maximum dosage that can used in ischemic stroke patients after the three hour window without any harm to the patient?. Additional randomized trials on this treatment are needed to improve the safety and efficacy of intravenous thrombolysis alteplase and to answer the remaining questions.
<table>
<thead>
<tr>
<th>Author</th>
<th>Published</th>
<th>Study Type</th>
<th>POP Size</th>
<th>Treatments Studied</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Validity (Jadad Score)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hacke, W.</td>
<td>2008</td>
<td>Randomized Control Trial</td>
<td>821</td>
<td>Intravenous Altelase (0.9 mg/kg) body weight</td>
<td>Placebo</td>
<td>Symptomatic intracerebral Hemorrhage</td>
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<tr>
<td>Stephan, D. Geoffrey, D.</td>
<td>2008</td>
<td>Randomized Control Trial</td>
<td>101</td>
<td>Alteplase 3-6 h after stroke onset</td>
<td>Placebo</td>
<td>Reperfusion &amp; attenuates infract growth</td>
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<tr>
<td>Martin, L.</td>
<td>2007</td>
<td>Cohort, open Label</td>
<td>74</td>
<td>tPA administered between 3 and 6 h after onset of stroke</td>
<td>MRI vs. CT imaging for tPA</td>
<td>Symptomatic intracerebral Hemorrhage</td>
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<td>Martin, K. Eric, J.</td>
<td>2006</td>
<td>Prospective Cohort</td>
<td>400</td>
<td>Patients treated with intravenous tPA</td>
<td>No tPA</td>
<td>Intracerebral Hemorrhage</td>
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<tr>
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<td>2008</td>
<td>Cohort</td>
<td>664</td>
<td>Intravenous alteplase (0.9 mg/kg) between 3 h and 4.5</td>
<td>tPA administered at 3 hour</td>
<td>Symptomatic intracerebral hemorrhage within 24h</td>
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<tr>
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<td>2007</td>
<td>Cohort</td>
<td>1210</td>
<td>MRI-based &amp; CT-based Thrombolytic Therapy in Acute Ischemic Stroke within and Behind the Established time Window</td>
<td>No tPA</td>
<td>NIHSS scores, Safety &amp; efficacy</td>
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<td></td>
</tr>
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**TABLE 1: Review of Matrix Articles**

TABLE II: Proportion of patients in the 3–4·5-h and within 3-h cohorts according to time from stroke onset to treatment.7
TABLE III: Main and additional outcomes for patients treated between 3 h and 4·5 h compared with those treated within 3 h.7

Data are n/N (%; 95% CI), unless otherwise indicated. All patients were in full compliance with other European summary of product characteristics criteria (SITS-ISTR data at Nov 15, 2007). SICH= symptomatic intracerebral hemorrhage. SITS-MOST= Safe Implementation of Thrombolysis in Stroke Monitoring Study. ECASS= European-Australasian Acute Stroke Study. NINDS= National Institute of Neurological Disorders and Stroke. mRS= modified Rankin scale.

Adjusted for age, sex, history of hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, congestive heart failure, previous stroke, independence before present stroke, smoking, aspirin treatment at stroke onset, baseline National Institutes of Health Stroke Scale score, baseline blood pressure, baseline blood glucose, bodyweight, alteplase, baseline antihypertensive therapy, and signs of current infarction on baseline imaging.

† Odds ratios were calculated by comparing 3–4·5 h versus within 3 h cohorts.
‡ Odds ratio not calculated since this was an additional analysis, not the main outcome.
References


