Safety of Intravenous Recombinant Tissue Plasminogen Activator for Treatment of Acute Ischemic Stroke: The Minnesota Experience

---

A Thesis Submitted to the Faculty of the Graduate School of the University of Minnesota by

Warren Manyara

In Partial Fulfillment of the Requirements for Degree of Master of Science

Faculty Advisor: Robert L. Kane

June 2011

Abstract

Background and Purpose

Intravenous recombinant tissue plasminogen activator (IV rt-PA) has been shown to reduce the likelihood of disability and death following an acute ischemic stroke by placebo-controlled, randomized clinical trials. We evaluated the safety of this treatment in routine clinical practice by analyzing frequencies and predictors of poor outcomes in patients treated within hospitals in Minnesota.

Methods

In a retrospective observational cohort study of 576 acute ischemic stroke patients treated with IV rt-PA from January 2008 to June 2010, we reviewed data from 21 hospitals contributing information on stroke admissions to the Minnesota Stroke Registry. We applied multivariate logistic regression to determine association of demographic characteristics, cardiovascular risk factors and stroke severity with symptomatic intracranial hemorrhage, serious systemic hemorrhage and inpatient death.

Results

Acute ischemic stroke patients administered IV rt-PA were slightly older than non-thrombolytic treatment patients and had significantly higher frequencies of atrial fibrillation, diabetes mellitus and medical history of previous stroke. 4.6% of IV rt-PA patients were diagnosed with symptomatic intracranial hemorrhage (sICH), 1.1% incurred systemic hemorrhage and 7.3% died during their hospitalization. In comparison, 4.7% of patients not treated with any rt-PA died in the hospital. After adjustment for demographic and clinical factors, significant predictors of sICH were National Institutes of Health Stroke Scale (NIHSS) Score OR: 1.14 (1.06 – 1.22), diabetes mellitus OR: 9.97 (1.32 – 75.21), dyslipidemia OR: 6.42 (1.35 – 30.51), hypertension OR: 5.57 (1.11 – 27.98) and medical history of a previous stroke OR: 5.32 (1.03 – 27.62). Higher NIHSS scores were associated with a greater risk of inpatient death. Intravenous thrombolysis 3 – 4.5 hours after stroke symptoms did not increase the risk for sICH or inpatient death when compared with IV rt-PA administration within 3 hours. Patients aged 80 years and older did not incur significantly different inpatient outcomes.

Conclusions

When compared to the frequencies of poor outcomes reported in clinical trials and previous observational studies, inpatient IV rt-PA clinical outcomes in Minnesota suggest this is a safe treatment. NIHSS Score, diabetes mellitus, dyslipidemia, hypertension and previous stroke are possible risk factors for post-thrombolytic cerebral hemorrhage.

Table of Contents

List of Tables

List of Figures

Background

Thrombolysis for treatment of acute ischemic stroke with intravenous recombinant tissue plasminogen activator (IV rt-PA) has been shown to improve clinical outcomes in randomized, placebo-controlled, double-blind clinical trials.[1, 2] Symptomatic intracranial hemorrhage (sICH) however occurred more frequently in the IV rt-PA group. This complication was associated with unfavorable functional outcome and death within three months of administration of IV rt-PA for acute stroke[3-5] and thus poses an important safety concern. Studies on the use of IV rt-PA in clinical practice have shown sICH incidence rates ranging from 2.7 – 15.7%.[6, 7] In this registry-based retrospective observational study, we evaluated the frequency of symptomatic intracranial hemorrhage in Minnesota as a measure of safety of IV rt-PA routine practice. Our study also evaluated possible demographic and cardiovascular risk factors associated with sICH. Information on these predisposing characteristics could enhance patient selection and management, potentially decreasing the likelihood of cerebral hemorrhage and associated decline in functional dependency and death.

As with sICH, the frequency of inpatient death following administration of IV rt-PA varies, and mortality as high as 25.4% has been observed.[8] A Nationwide Inpatient Sample study identified advanced age, congestive heart failure, atrial fibrillation/flutter and the presence of diabetes mellitus as risk factors of inpatient mortality in acute ischemic stroke patients treated with thrombolysis.[9] Differences in the distribution of patient characteristics likely account for much of this variation, cohorts comprised of patients with more risk factors for sICH are likely to experience higher frequencies of post-thrombolytic cerebral hemorrhage. Protocol deviations have also been implicated in higher death rates.[8] Major protocol deviations such as incorrect IV rt-PA dosing, administration of IV rt-PA in patients who have incurred head injuries in the past three months, or in patients with hypertensive urgency at the time of treatment has been associated with high inpatient mortality rates.[8]

Clinical trials as well as observational studies have shown lower frequencies of systemic hemorrhage than sICH in patients receiving IV rt-PA for ischemic strokes.[1, 4, 10] Low incidences of this complication generally does not allow extensive analyses of the outcome.

In May 2009, a science advisory from the American Heart Association/American Stroke Association (AHA/ASA) recommended extending the time limit in which IV rt-PA may be

administered following stroke onset from 3 hours to 4.5 hours in ischemic stroke patients meeting specific criteria.[11] The recommendation followed publication of results from the European Cooperative Acute Stroke Study (ECASS) III, a randomized clinical trial which showed that ischemic stroke patients administered IV rt-PA between 3 and 4.5 hours after the onset of stroke symptoms demonstrated significantly improved clinical outcomes at 90 days compared with the placebo-treated group. The change was also supported by an observational study of patients treated in clinical practice that compared clinical outcomes of 664 patients treated with IV rt-PA 3 – 4.5 hours after onset of stroke symptoms with 11 865 patients treated within 3 hours.[12] This study found no differences in clinical outcomes between the two treatment groups when comparing adjusted odds of symptomatic intracranial hemorrhage, and mortality and independence three months from treatment. We evaluated the safety of IV rt-PA treatment during this extended window for patients treated in Minnesota by comparing the likelihood of poor outcomes for this group with those receiving thrombolytic treatment within three hours. Comparison of complication rates was also done with those reported in clinical trials.

Information on clinical outcomes for acute ischemic stroke patients older than 80 years treated with IV rt-PA is limited. The ECASS III clinical trial[2] excluded patients over 80 years old and the current AHA/ASA guidelines for treatment of ischemic stroke patients presenting 3 – 4.5 hours after onset of symptoms recommend against use of IV rt-PA in patients older than 80 years owing to scarcity of information on efficacy in this age group.[11] A number of observational studies have been conducted comparing the frequencies and likelihood of post-thrombolytic cerebral hemorrhage, inpatient death, functional outcome and mortality on interval follow-up in patients over the age of 80 years treated with IV rt-PA with those below 80 years of age. In the Canadian Alteplase for Stroke Effectiveness Study (CASES), the risk of symptomatic intracerebral hemorrhage did not differ significantly between IV rt-PA ischemic stroke patients 80 years and older and those younger than 80 years, but the likelihood of excellent outcome(modified Rankin Score 0 – 1 at 90 days) in patients 80 years and above was significantly lower.[13] An observational study of IV rt-PA treatment outcomes at three German medical centers compared those 80 years and older with younger patients and showed no differences in sICH, and lower frequency of favorable outcome (mRS 0 – 1) and a higher death rate at 90 days of follow up.[14] Similarly, an analysis of the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) database found comparable likelihood of sICH but lower

independence and greater mortality in patients older than 80 years compared to younger patients.[15] In an effort to contribute to knowledge on the clinical outcomes of older stroke patients treated with thrombolysis, this study evaluated the likelihood of inpatient death and sICH in patients 80 years and older.

Patients and Methods

Description of Database

The Minnesota Stroke Registry is a part of the Centers for Disease Control and Prevention Paul Coverdell National Acute Stroke Registry (PCNASR) program.[16] Data from stroke admissions and treatment are collected from participant hospitals and monitored in order to provide feedback that enables improvements in the delivery of care to patients with acute stroke. Trained abstractors use one of two internet-based data collection tools to acquire and enter stroke registry data: The Minnesota Stroke Registry Tool (MSRT) created and maintained by the Minnesota Department of Health, or the American Heart Association Get With The Guidelines-Stroke Patient Management Tool (GWTG-Stroke PMT, Outcome Sciences Inc, Cambridge, Massachusetts).[17] Approximately 40% of cases are entered directly into the MSRT and the rest are entered through the GWTG-Stroke PMT. The Minnesota Stroke Registry began in January 2008 with 13 hospitals, and as of 2011 involves 34 hospitals.

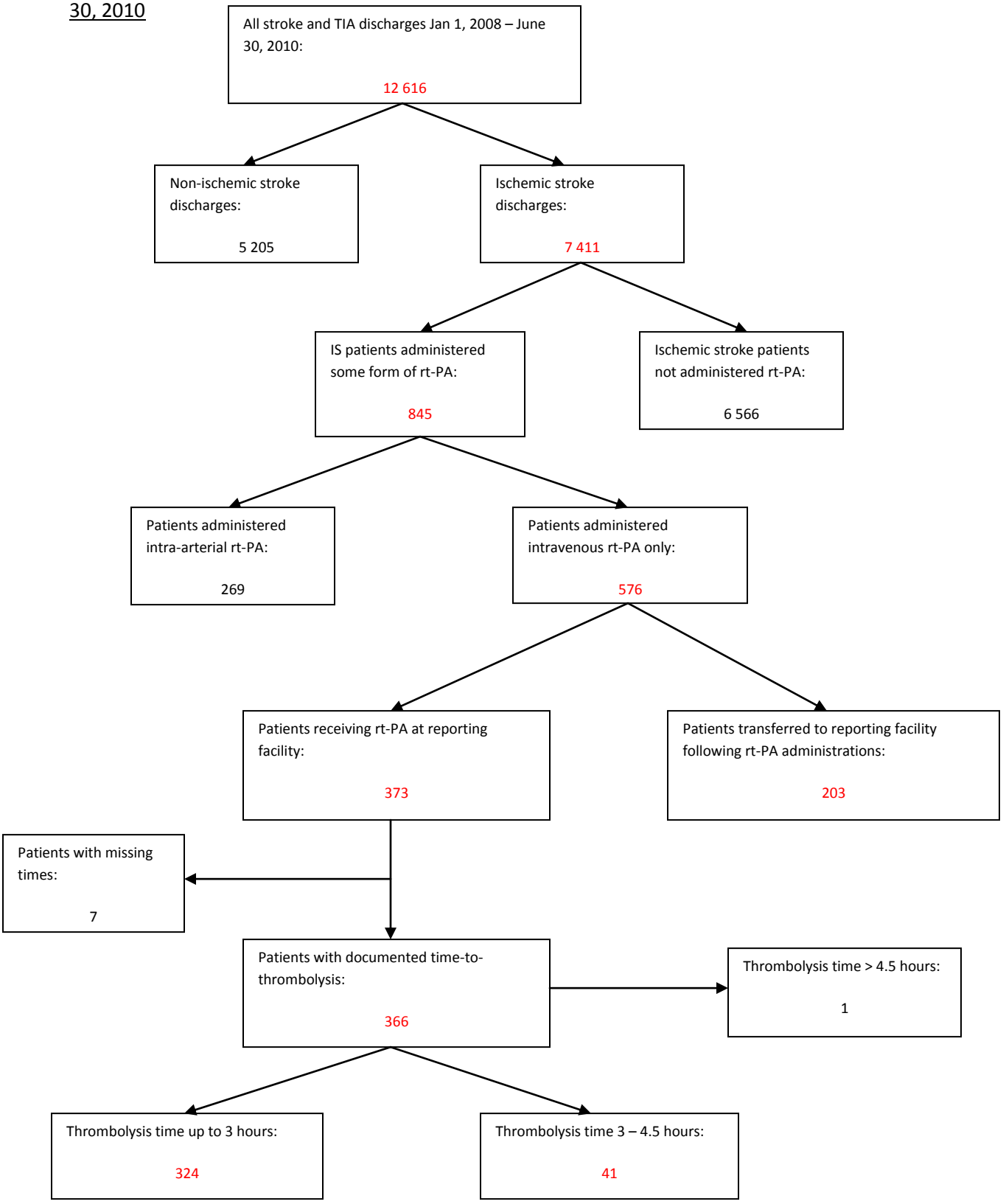
Data validation and quality assurance procedures have been implemented to ensure accuracy of the information collected. Chart audits are conducted annually by a trained quality assurance abstraction coordinator for quality control using random chart selection. Select key data elements are audited among a sample of cases, and appropriate analyses are conducted to validate data abstraction. Where discrepancies occur, possible changes are considered including modifications of abstraction tools and training.

Study Cohort

A study cohort was created including all patients in the Minnesota Stroke Registry with a final diagnosis of stroke or transient ischemic attack (TIA) with hospital discharge dates from January 1, 2008 to June 30, 2009. These patients were seen at 21hospitals throughout Minnesota, rural and urban, teaching and non-teaching. The total number of patients was 12 616. Patients with a diagnosis of ischemic stroke were then selected totaling 7 411. Of the ischemic stroke patients, 576 were treated with intravenous rt-PA as the only form of thrombolytic treatment (IV rt-PA patients). 203 IV rt-PA patients were administered intravenous thrombolysis at an outside facility before transfer to a reporting facility. The Minnesota Stroke Registry did not capture symptom onset or treatment times for these patients. 373 patients were treated with IV rt-PA at a reporting facility and 63.8% of them had a documented NIHSS score, a measure of

stroke severity that assesses presence of clinical features such as level of consciousness, facial and limb weakness. 324 patients treated at a reporting facility were administered IV rt-PA within 3 hours of onset of stroke symptoms and 41 patients received treatment after 3 hours up to 4.5 hours. One patient was documented to have received IV-rt more than 4.5 hours after initial stroke symptoms. A diagram showing patient diagnoses and treatment is outlined in figure 1.

Figure 1. Minnesota Stroke Registry Patient Diagnoses and Treatment January 1, 2008 to June 30, 2010



Demographic Characteristics and Cardiovascular Risk Factors

We analyzed information on demographic characteristics that we deemed most salient to ischemic stroke outcomes: age, sex and race. In the study protocol, we elected to analyze information on cardiovascular risk factors with prevalence exceeding 5% of the study cohort. These were atrial fibrillation/flutter, coronary artery disease/prior myocardial infarction, carotid stenosis, diabetes mellitus, dyslipidemia, heart failure, hypertension, peripheral artery disease, medical history of previous stroke, and medical history of previous transient ischemic attack. We then considered possible interaction between co-morbidities that could potentially influence the association of the different cardiovascular risk factors with the outcomes and adjusted for this possible effect modification. Patients' total number of cardiovascular risk factors was also evaluated as a possible predictor of poor IV rt-PA outcomes.

Clinical Outcome Measures

To assess the safety of IV rt-PA, we reviewed data on the occurrence of poor outcomes that have been reported for IV rt-PA in treatment of acute ischemic stroke in clinical trials: sICH, serious systemic hemorrhage and inpatient death.[1, 2] The Minnesota Stroke Registry designates sICH and life-threatening, serious systemic hemorrhage that occur within 36 hours of thrombolytic therapy as complications of the treatment. In practice, symptomatic intracranial hemorrhage is confirmed by imaging, usually a computed tomography (CT) scan, in patients that deteriorate neurologically following rt-PA administration. If the pre-treatment imaging did not demonstrate an intracranial bleed, and a new area of hemorrhage is discovered on the scan following neurological deterioration, then the new bleed is attributed to rt-PA administration. Extracranial hemorrhage within 36 hours of rt-PA administration that is deemed life-threatening by treating physicians is considered serious systemic hemorrhage. Given that a patient met criteria for rt-PA administration and did not have underlying active bleeding, recent history of gastrointestinal or urinary tract hemorrhage, an elevated activated partial thromboplastin time (aPTT) or international normalized ratio (INR) above 1.7, then new hemorrhage is likely a result of IV rt-PA administration.

Statistical Analysis

The univariate procedure was used to calculate the distribution of continuous variables in the study population (age, total number of cardiovascular risk factors and NIHSS scores). We applied the t-test to compare continuous variables between groups. The chi-square test was used for calculating the distribution of categorical variables: age in six groups, under 40 years, 40 – 49, 50 – 59, 60 – 69, 70 – 79 and 80 and above; sex; and race, White, Black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaskan Native and other race. In order to assess whether IV rt-PA patients with a documented NIHSS score differed from those without, we compared the demographic and cardiovascular risk factors for the two groups (table 1). We further performed univariate logistic regression to evaluate if presence of the NIHSS score was associated with the safety outcomes using an indicator variable to denote documented and missing NIHSS scores. Documentation of the NIHSS score was not significantly associated with either of the outcomes: sICH OR: 0.88 (0.40 – 1.95), p = 0.759 and death OR: 0.67 (0.36 – 1.25), p = 0.207. Pre-planned logistic regression models were used to compute the association of predictors with sICH and death. The logistic regression model applied to estimate the likelihood of sICH comprised the following predictors: age, sex, race White v. non-White, the indicator variable for the presence or absence of NIHSS score, NIHSS score, history of hypertension, transient ischemic attack, coronary artery disease or myocardial infarction, diabetes mellitus, atrial fibrillation/flutter, previous stroke, dyslipidemia, total number of cardiovascular risk factors, possible interaction between diabetes mellitus and previous stroke, diabetes mellitus and coronary artery disease and interaction between diabetes mellitus and dyslipidemia. Likelihood of inpatient death was calculated with a logistic regression model that included the variables in the sICH model plus medical history of carotid stenosis and heart failure. The variable for interaction between diabetes mellitus and previous stroke was excluded where it compromised the validity of the prediction model showing an extremely wide confidence interval for the OR estimate of the interaction term. Significance of association between predictor and outcome variables was tested at the 0.05 threshold. Statistical computations were performed with SAS version 9.2 software (SAS Institute, Cary, North Carolina).

Results

Patient Characteristics

From January 1, 2008 to June 2010, 576 acute ischemic stroke patients received IV rt-PA as the only form of thrombolytic treatment. Mean age in the IV rt-PA group was 73.0 years ± 0.57 (SE). 36.1% of the patients were 80 years or older. Women made up 48.4% of the group. 80.9% self-reported as White (table 1). Hypertension was the most common cardiovascular risk factor occurring in 71.2% of IV rt-PA ischemic stroke patients. The mean total number of cardiovascular risk factors was similar in both ischemic stroke IV rt-PA patients and non-rt-PA patients. Patients who were treated with IV rt-PA tended to have more severe stroke presentations than patients not treated with thrombolytic therapy, however this comparison is limited by missing NIHSS score documentation. Patients who were treated with IV rt-PA at an outside facility before transferring to a reporting facility were similar in demographic and clinical characteristics to those treated at a reporting facility, except that outside facilities had a higher proportion of White patients (table 1). A racial difference was also noted in comparing characteristics of IV rt-PA patients with a documented NIHSS score with those without; there was a higher proportion of White patients in the group without NIHSS scores. No significant differences in patient characteristics were observed when comparing IV rt-PA patients treated within three hours of symptom onset with those treated within 3 to 4.5 hours.

Frequencies of Poor Outcomes and Association of Predictors with Complications and Death

A total of 576 acute ischemic stroke patients received IV rt-PA. Twenty six (4.6%) incurred sICH and 42 (7.3%) died while hospitalized (table 2). In comparison, 4.7% of patients not treated with any rt-PA in this cohort died. Information on time onset of symptoms or IV thrombolysis treatment was unavailable for patients that were transferred to a reporting facility having received IV rt-PA at an outside hospital. 98.1% of IV rt-PA patients treated at a reporting facility had recorded symptom onset and treatment times and were stratified patients into three groups; treated within three hours, after three hours up to 4.5 hours and treated after 4.5 hours. Those treated 3 – 4.5 hours after onset of symptoms at a reporting facility had lower frequencies of sICH and inpatient death than those treated within three hours of onset of stroke symptoms.

Table 1. Distribution of Demographic and Clinical Characteristics by Study Groups

	Ischemic stroke patients	IV rt-PA given at reporting facility	IV rt-PA given at outside facility	p-value	IV rt-PA patients with NIHSS score	IV rt-PA patients without NIHSS score	p-value	Reporting Facility		p-value
								rt-PA t =< 3 hours	rt-PA 3 < t =<4.5 hours	
	n = 7411	n = 373	n = 203		n = 328	n = 248		n =324	n =41	
Age										
Mean, y (± SE)	71.2 (± 0.17)	72.5 (± 0.73)	73.9 (± 0.89)	0.249	72.0 (± 0.79)	74.2 (± 0.79)	0.064	72.5 (± 0.79)	71.7 (± 1.98)	0.726
Median, y (IQR)	74.0 (61 – 83)	74 (64 – 84)	76 (65 – 84)		74 (63 – 82.5)	76 (64.5 – 85)		74 (64 – 84)	74 (64 – 81)	
< 40	2.7	1.9	1.0		2.7	0.0		2.2	0.0	
40 – 49	6.2	4.8	2.5		4.6	3.2		4.3	7.3	
50 – 59	13.7	11.8	11.3	0.733	11.9	11.3	0.109	11.7	14.6	0.311
60 – 69	18.8	18.2	18.7		18.3	18.6		19.1	9.8	
70 – 79	23.1	27.6	29.6		29.0	27.4		26.9	39.0	
≥ 80	35.6	35.7	37.0		33.5	39.5		35.8	29.3	
Sex (%)										
M	48.3	50.7	53.2	0.561	52.7	50.0	0.514	48.8	63.4	0.077
F	51.7	49.3	46.8		47.3	50.0		51.2	36.6	
Race (%)										
White	79.5	75.3	91.1		76.5	86.7		75.3	75.61	
Black or AA	4.4	4.3	0.0		4.3	0.8		4.6	0.0	
Asian	2.6	2.7	0.0		2.4	0.8		2.2	7.3	
Native Hawaii/Pac Isla	0.6	0.3	0.0		0.3	0.0		0.0	2.4	
Am Indi/Alaska native	0.4	0.5	0.5		0.6	0.4		0.6	0.0	
Other	0.6	0.3	0.0		0.3	0.0		0.3	0.0	
Co-morbidities (%)										
A-fib/A-flutter	21.3	26.3	22.7	0.339	25.6	24.2	0.698	26.9	24.4	0.737
CAD/Prior MI	26.3	30.6	27.1	0.382	26.2	33.5	0.059	30.9	26.8	0.597
Carotid stenosis	5.4	5.1	4.9	0.930	5.2	4.8	0.852	4.9	4.9	1.000
Diabetes mellitus	26.2	20.1	21.7	0.657	21.7	19.4	0.501	19.4	24.4	0.456
Dyslipidemia	47.8	46.7	47.3	0.883	45.1	49.2	0.332	45.4	56.1	0.195
Heart failure	9.9	12.1	7.9	0.119	11.6	9.3	0.372	12.4	9.8	0.801
Hypertension	73.5	70.8	71.9	0.772	70.4	72.2	0.646	69.4	80.5	0.143
PAD	6.4	8.6	5.9	0.250	6.7	8.9	0.333	8.0	12.2	0.367
Previous stroke	17.2	15.0	10.8	0.162	16.8	9.3	0.009	15.4	9.8	0.335
Previous TIA	6.3	7.5	5.4	0.341	7.0	6.5	0.793	7.4	7.3	1.000
Total co-morbidities mean (±SE)	2.4 (± 0.02)	2.4 (± 0.09)	2.3 (±0.10)	0.179	2.4 (± 0.09)	2.4 (± 0.10)	0.982	2.4 (± 0.09)	2.6 (± 023)	0.540
NIHSS (Mean ±SE)*	6.4 (± 0.15)	10.8 (± 0.51)	10.6 (± 0.77)	0.837	-----	-----	-----	11.0 (± 0.54)	9.0 (± 1.74)	0.259

*NIHSS score documentation for the patient groups: Ischemic stroke patients – 36.0%, IV rt-PA patients – 56.9%, patients given IV rt-PA at reporting facility – 63.8%, patients given IV rt-PA at outside facility – 44.3%, IV rt-PA patients receiving treatment up to three hours from onset of stroke symptoms – 64.8%, IV rt-PA patients receiving treatment 3 – 4.5 hrs after onset of stroke symptoms – 56.1%.

Table 2. Frequencies of Hemorrhage 36 hours After rt-PA Administration and Inpatient Death

	Patients with Symptomatic Intracranial Hemorrhage n (%)	**Patients with Life-threatening Systemic Hemorrhage** n (%)	**Patients who Died Inpatient Following rt-PA Treatment** n (%)
IV rt-PA patients, 576	26 (4.6)	6 (1.1)	42 (7.3)
IV rt-PA at outside facility, 203	8 (4.0)	1 (0.5)	14 (6.9)
IV rt-PA at reporting facility within 3 hours, 324	16 (5.1)	4 (1.3)	25 (7.7)
IV rt-PA at reporting facility 3 – 4.5 hours, 41	1 (2.6)	1 (2.6)	2 (4.9)
IV rt-PA at reporting facility with unknown onset-to-treatment times, 7	1 (14.3)	0	1 (14.3)

Calculations of percentages exclude patients in each group with unknown outcomes.

After adjustment for demographic and clinical characteristics including possible interaction between diabetes mellitus and CAD/previous MI, and between diabetes mellitus and dyslipidemia, the severity of the stroke as measured by the NIHSS and four cardiovascular risk factors were significant predictors of sICH; diabetes mellitus OR: 9.97 (1.32 – 75.21), dyslipidemia OR: 6.42 (1.35 – 30.51), hypertension OR: 5.57 (1.11 – 27.98) and medical history of previous stroke OR: 5.32 (1.03 – 27.62) (table 3). Neither age, sex nor race was a significant predictor of sICH. When age was modeled as a dichotomous variable with patients 80 years and older compared with younger patients, IV rt-PA treated stroke patients 80 years and older did not show significantly different odds of sICH OR: 0.74 (0.30 – 1.86) or death 1.14 (0.55 – 2.36). Increasing NIHSS score was the only identified predictor of inpatient death OR: 1.15 (1.08 – 1.23). Patients treated with IV rt-PA 3 – 4.5 hours after onset of stroke symptoms did not show significantly different odds of sICH or systemic hemorrhage after adjustment for demographic and cardiovascular risk factors (table 4). The pre-planned logistic regression model for predicting serious systemic hemorrhage did not provide reliable estimates due to the low incidence of events.

Table 3. Multivariate-adjusted Odds Ratios for Association of Demographic Characteristics and Cardiovascular Risk Factors with IV rt-PA Poor Outcomes

	Symptomatic intracranial hemorrhage	p-value	Inpatient death	p-value
	OR (95% CI)		OR (95% CI)	
Age , y	0.99 (0.95 – 1.03)	0.543	1.02 (0.99 – 1.05)	0.177
Sex Female v. Male	0.88 (0.36 – 2.14)	0.775	0.79 (0.38 – 1.65)	0.535
Race White v. Non-white	1.26 (0.41 – 3.82)	0.685	0.76 (0.31 – 1.82)	0.533
Cardiovascular risk factors				
A-fib/A-flutter	4.08 (0.98 – 16.97)	0.053	3.20 (0.70 – 14.68)	0.134
CAD/Prior MI	2.18 (0.43 – 11.12)	0.347	3.73 (0.72 – 19.25)	0.116
Carotid stenosis	-----		6.37 (0.87 – 46.72)	0.069
Diabetes mellitus	9.97 (1.32 – 75.21)	0.026	1.44 (0.17 – 12.44)	0.739
Dyslipidemia	6.42 (1.35 – 30.51)	0.019	1.27 (0.25 – 6.47)	0.770
Heart Failure	-----		3.61 (0.64 –20.31)	0.146
Hypertension	5.57 (1.11 – 27.98)	0.037	3.70 (0.71 – 19.36)	0.122
Previous stroke	5.32 (1.03 – 27.62)	0.047	1.99 (0.33 – 11.88)	0.451
Previous TIA	1.32 (0.12 – 14.40)	0.821	0.74 (0.06 – 9.28)	0.816
Number of CV risk factors	0.41 (0.14 – 1.17)	0.094	0.48 (0.12 – 1.89)	0.296
NIHSS Score	1.14 (1.06 – 1.22)	0.001	1.15 (1.08 – 1.23)	<0.001

Table 4. Association of Time-to-treatment with Complications Adjusted for Demographic Characteristics and Cardiovascular Risk Factors

	Symptomatic intracranial hemorrhage		Inpatient death	
	OR (95% CI)		OR (95% CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
IV rt-PA within 3 hours	1.0	1.0	1.0	1.0
IV rt-PA given 3 – 4.5 hours	0.49 (0.06 – 3.80)	0.41 (0.05 – 3.38)	0.61 (0.14 – 2.69)	0.66 (0.12 – 3.49)
p-value	0.487	0.408	0.514	0.620

Adjusted ORs from multivariate logistic regression model including age, sex, race White v. non-White, the indicator variable for the presence or absence of NIHSS score, NIHSS score, history of hypertension, transient ischemic attack, coronary artery disease or myocardial infarction, diabetes mellitus, atrial fibrillation/flutter, previous stroke, dyslipidemia, total number of cardiovascular risk factors and interaction terms diabetes mellitus*coronary artery disease and diabetes mellitus*dyslipidemia.

Discussion

In a systematic review that evaluated risk factors of sICH following thrombolytic therapy for treatment of acute ischemic stroke, diabetes mellitus was identified as a significant predictor in six of the twelve studies.[18] Our study found that patients with diabetes mellitus had greater than nine times the odds of sICH within 36 hours of IV rt-PA compared to acute ischemic patients without diabetes ($p = 0.03$). A myriad of hyperglycemic pathophysiological mechanisms have been described that possibly exert an overall risk for sICH.[19] An MRI-based study of the effect of hyperglycemia on acute stroke outcomes found that patients with hyperglycemia at the time of presentation had less recovery of penumbra tissue and larger infarcts.[20] The effect of acute hyperglycemia on the risk of sICH relative to the impact of chronic vascular changes caused by diabetes mellitus remains unknown.

Dyslipidemia is considered a risk factor for ischemic stroke,[21-23] however, its influence on the risk of sICH following IV rt-PA is not well described in literature. We postulate that cerebrovascular atherosclerosis associated with dyslipidemia results in poor recanulation following intravenous thrombolytic treatment and contributes to hemorrhagic transformation.

The change in IV rt-PA treatment guidelines recommending thrombolysis in patients 3 – 4.5 hours after symptom onset[11] presents safety questions regarding the outcomes of patients treated within the extended window in clinical practice. A prospective cohort study conducted in Groningen, The Netherlands found no significant differences in the outcomes between IV rt-PA patients treated within three hours and those treated 3 – 4.5 hours in terms of sICH, death within a week from admission and independent functioning at three months (mRS 0 – 2).[24] Our study of inpatient outcomes for IV rt-PA treatment times also did not demonstrate a difference between the three hour and the 3 – 4.5 hour groups. However, the 3 – 4.5 hour patient sample was small, $n = 41$, resulting in wider confidence intervals. Perhaps the number of people who received IV rt-PA 3 – 4.5 hours after the onset of stroke symptoms is small in part because the recommendation for expansion of the window for treatment of acute ischemic stroke with IV rt-PA was issued well into our study period.

Increasing age was not a significant predictor of sICH or inpatient death in our study. When we substituted age in the logistic regression models with a variable comparing patients 80 years and older with younger patients, there was no significant difference between the two groups in their

likelihood of sICH or inpatient death after adjustment for covariates. These findings are not inconsistent with studies that have shown higher mortality and greater likelihood of functional dependence at three months in IV rt-PA patients 80years and older.[13-15, 25] This study did not involve follow up beyond hospital discharge.

Establishing acceptable frequencies of complications is of a matter of interest to clinicians. A number of studies of rt-PA thrombolysis for acute ischemic stroke in clinical practice use rates of sICH reported in clinical trials for comparison; the NINDS rt-PA study treatment group incurred a sICH rate of 6.4% within 36 hours of IV rt-PA administration and subjects in the ECASS III study had a 2.4% rate of sICH.[1, 2] One challenge to comparison is that the methods of assessment for sICH were somewhat different between these two clinical trials; the NINDS study designated any neurological deterioration associated with intracranial hemorrhage as sICH whereas the ECASS III study set a threshold of neurological decline of four points or more on the NIHSS, or death attributable to an intracranial bleed. Perhaps more importantly, differences in patient characteristics connote dissimilarity in risk of sICH. While the proportion of patients in the Minnesota study who incurred sICH is low, 4.6%, this incidence should be considered along with the likely variation in sICH definitions between clinicians and institutions, as well as a potential underreporting bias stemming from rare routine follow-up imaging protocols in clinical practice.

This study showed a higher crude inpatient mortality in patients that underwent IV rt-PA treatment in comparison to patients that did not undergo any thrombolytic treatment, 7.3% and 4.7% respectively. The crude inpatient mortality attributable to IV rt-PA would thus be about 2.6%. A Nationwide Inpatient Sample study from 1999 – 2002 also found a higher proportion of deaths in acute ischemic stroke patients treated with rt-PA compared with non-thrombolytic treated patients, 11.4% to 6.8%.[9] These proportions, however, do not take into account a likely higher stroke severity in patients treated with IV rt-PA in comparison to non-treated patients. Importantly, clinical trials have shown an overall higher survival at 3 months follow up in patients treated with IV rt-PA compared to placebo-treated cohorts.[1, 2]

Our ability to compare the likelihood of poor outcomes between patients treated with IV rt-PA within three hours of stroke onset and those treated 3 – 4.5 hours after manifestation of stroke symptoms is hindered by the small sample sizes as well as the low frequency of events. In order to detect a significant difference in the likelihood of sICH with 90% power at the 0.05 level of significance, at least 11 events would be needed in two groups of equal size. Given a rate of

sICH of 2.6% in the group receiving IV rt-PA 3 – 4.5 hours after symptom onset, a sample of 424 patients would be needed for each group.

The registry-based nature of our study imposes some limitations. In the absence of inpatient charts, our ability to formulate important associations and seek clarifications is limited. While the hemorrhagic outcomes were specifically linked to IV rt-PA administration in the abstraction, our assignment of death as a complication involves some uncertainty. Because information in the Minnesota Stroke Registry does not specify the cause of death, we are not able to identify patients, if any, who died from causes not related to stroke or rt-PA administration. Further, the long-term outcomes of this cohort are unknown. A large prospective observational study particularly focusing on patients receiving IV rt-PA 3 – 4.5 hours after stroke administration would be helpful in further evaluating the safety of IV rt-PA for treatment of ischemic stroke patients in clinical practice.

References

1. Tissue plasminogen activator for acute ischemic stroke. the national institute of neurological disorders and stroke rt-PA stroke study group. N Engl J Med 1995 Dec 14;333(24):1581-7.

2. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D, ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008 Sep 25;359(13):1317-29.

3. Kohrmann M, Juttler E, Fiebach JB, Huttner HB, Siebert S, Schwark C, Ringleb PA, Schellinger PD, Hacke W. MRI versus CT-based thrombolysis treatment within and beyond the 3 h time window after stroke onset: A cohort study. Lancet Neurol 2006 Aug;5(8):661-7.

4. Hill MD, Buchan AM, Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: Results of the canadian alteplase for stroke effectiveness study. CMAJ 2005 May 10;172(10):1307-12.

5. Simon JE, Sandler DL, Pexman JH, Hill MD, Buchan AM, Calgary Stroke Programme. Is intravenous recombinant tissue plasminogen activator (rt-PA) safe for use in patients over 80 years old with acute ischaemic stroke? - the calgary experience. Age Ageing 2004 Mar;33(2):143-9.

6. Koennecke HC, Nohr R, Leistner S, Marx P. Intravenous tPA for ischemic stroke team performance over time, safety, and efficacy in a single-center, 2-year experience. Stroke 2001 May;32(5):1074-8.

7. Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA, Hammel JP, Qu A, Sila CA. Use of tissue-type plasminogen activator for acute ischemic stroke: The cleveland area experience. JAMA 2000 Mar 1;283(9):1151-8.

8. Bravata DM, Kim N, Concato J, Krumholz HM, Brass LM. Thrombolysis for acute stroke in routine clinical practice. Arch Intern Med 2002 Sep 23;162(17):1994-2001.

9. Bateman BT, Schumacher HC, Boden-Albala B, Berman MF, Mohr JP, Sacco RL, Pile-Spellman J. Factors associated with in-hospital mortality after administration of thrombolysis in acute ischemic stroke patients: An analysis of the nationwide inpatient sample 1999 to 2002. Stroke 2006 Feb;37(2):440-6.

10. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: The standard treatment with alteplase to reverse stroke (STARS) study. JAMA 2000 Mar 1;283(9):1145-50.

11. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP,Jr, American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: A science advisory from the american heart Association/American stroke association. Stroke 2009 Aug;40(8):2945-8.

12. Wahlgren N, Ahmed N, Davalos A, Hacke W, Millan M, Muir K, Roine RO, Toni D, Lees KR, SITS investigators. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): An observational study. Lancet 2008 Oct 11;372(9646):1303-9.

13. Sylaja PN, Cote R, Buchan AM, Hill MD, Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis in patients older than 80 years with acute ischaemic stroke: Canadian alteplase for stroke effectiveness study. J Neurol Neurosurg Psychiatry 2006 Jul;77(7):826-9.

14. Berrouschot J, Rother J, Glahn J, Kucinski T, Fiehler J, Thomalla G. Outcome and severe hemorrhagic complications of intravenous thrombolysis with tissue plasminogen activator in very old (> or =80 years) stroke patients. Stroke 2005 Nov;36(11):2421-5.

15. Ford GA, Ahmed N, Azevedo E, Grond M, Larrue V, Lindsberg PJ, Toni D, Wahlgren N. Intravenous alteplase for stroke in those older than 80 years old. Stroke 2010 Nov;41(11):2568-74.

16. CDC State Heart Disease and Stroke Prevention Programs [Internet]Atlanta, Georgia: Centers for Disease Control and Prevention; c2011 [cited 2011 3/5]. Available from: http://www.cdc.gov/dhdsp/programs/stroke_registry.htm.

17. George MG, Tong X, McGruder H, Yoon P, Rosamond W, Winquist A, Hinchey J, Wall HK, Pandey DK, Centers for Disease Control and Prevention (CDC). Paul coverdell national acute stroke registry surveillance - four states, 2005-2007. MMWR Surveill Summ 2009 Nov 6;58(7):1-23.

18. Lansberg MG, Albers GW, Wijman CA. Symptomatic intracerebral hemorrhage following thrombolytic therapy for acute ischemic stroke: A review of the risk factors. Cerebrovasc Dis 2007;24(1):1-10.

19. Alvarez-Sabin J, Molina CA, Montaner J, Arenillas JF, Huertas R, Ribo M, Codina A, Quintana M. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator--treated patients. Stroke 2003 May;34(5):1235-41.

20. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM. Acute hyperglycemia adversely affects stroke outcome: A magnetic resonance imaging and spectroscopy study. Ann Neurol 2002 Jul;52(1):20-8.

21. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA, American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: A guideline for healthcare professionals from the american heart Association/American stroke association. Stroke 2011 Feb;42(2):517-84.

22. Iso H, Jacobs DR,Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N Engl J Med 1989 Apr 6;320(14):904-10.

23. Lindenstrom E, Boysen G, Nyboe J. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: The copenhagen city heart study. BMJ 1994 Jul 2;309(6946):11-5.

24. Uyttenboogaart M, Koch MW, Koopman K, Vroomen PC, De Keyser J, Luijckx GJ. Safety of antiplatelet therapy prior to intravenous thrombolysis in acute ischemic stroke. Arch Neurol 2008 May;65(5):607-11.

25. Engelter ST, Bonati LH, Lyrer PA. Intravenous thrombolysis in stroke patients of > or = 80 versus < 80 years of age--a systematic review across cohort studies. Age Ageing 2006 Nov;35(6):572-80.