Real-World Outcomes of Acute Ischemic Stroke Treatment with Intravenous Recombinant Tissue Plasminogen Activator

Keith A. Betts, PhD,* Dana Hurley, PharmD,† Jinlin Song, PhD,* Gautam Sajeev, ScD,‡ Jenny Guo, MS,‡ Ella Xiaoyan Du, MSc,* Marco Paschoalin, MD,§ and Eric Q. Wu, PhD‡

Background and Purpose: In clinical trials, intravenous (IV) recombinant tissue-type plasminogen activator (rt-PA) reduces the likelihood of disability if given within 3 hours of acute ischemic stroke. This study compared real-world outcomes between patients treated and patients not treated with IV rt-PA. *Methods:* In this retrospective study, United States–based neurologists randomly selected eligible acute ischemic stroke patients from their charts who were and were not treated with IV rt-PA. Mortality, hospital readmission, and independence were compared between patients treated and patients not treated with IV rt-PA using Kaplan–Meier curves, log-rank tests, and Cox proportional hazards models. *Results:* A total of 1026 charts were reviewed with a median follow-up time of 15.5 months. Pretreatment stroke severity, as measured by the National Institutes of Health Stroke Scale, was comparable between cohorts (IV rt-PA =11.7; non-rt-PA = 11.3; $P = .165$). IV rt-PA patients experienced significantly longer survival ($P = .013$), delayed hospital readmission ($P = .012$), and shorter time to independence ($P < .001$) compared with patients not treated with rt-PA. After adjusting for baseline characteristics, IV rt-PA patients had significantly lower mortality (hazard ratio [95% confidence interval] = .52 [.30, .90]) and greater rates of independence (hazard ratio [95% confidence interval] = 1.42 [1.17, 1.71]) than patients not treated with rt-PA. *Conclusions:* This real-world study indicated that acute ischemic stroke patients treated with IV rt-PA experience long-term clinical benefits in survival and functional status.

Key Words: Ischemic stroke—quality and outcomes—mortality/survival—recombinant tissue plasminogen activator.

From the *Analysis Group, Inc., Los Angeles, California; †HUTH Global, LLC, Seattle, Washington; ‡Analysis Group, Inc., Boston, Massachusetts; and §Genentech, South San Francisco, California.

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Address correspondence to Keith A. Betts, PhD, 333 South Hope St, 27th Floor, Los Angeles, CA 90071. E-mail: Keith.Betts@analysisgroup.com.

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Introduction

In the United States, approximately 795,000 people experience a new or recurrent stroke each year, with ischemic stroke accounting for nearly 90% of all strokes.[1] Despite the death rate from stroke falling nearly 34% over the past decade, stroke remains the fifth leading cause of death in the United States[2] and a major contributor to years lived with disability.[3] Stroke also incurs a large economic burden, with direct and indirect costs estimated to exceed $33 billion in the United States in 2012.[1]

Thrombolysis with intravenous (IV) recombinant tissue-type plasminogen activator (rt-PA) is the only U.S. Food and Drug Administration–approved treatment for acute ischemic stroke and is endorsed by the American Heart Association/American Stroke Association if administered within a tight time window after symptom onset (3 hours for most eligible patients and up to 4.5 hours for patients meeting additional eligibility criteria).[4,5] In randomized controlled trials, administration of IV rt-PA within 3 hours has shown efficacy in improving functional status, including an absolute increase of 10% in the likelihood of having no significant disability at 3-6 months[6-8]; after 3 hours, the benefit is less clear.[9] These trials have also reported that patients have a greater risk of death within the first 7 to 10 days after IV rt-PA administration, largely due to the increased occurrence of fatal intracranial hemorrhage.[7] Despite this initially elevated risk, the comparable mortality rates between patients treated with IV rt-PA and the control group at the end of follow-up (typically 3 months) in the clinical trials indicated lower mortality among patients treated with IV rt-PA in the subsequent period.[7] Consequently, several exclusion criteria limit the eligibility for IV rt-PA treatment to a subset of acute ischemic stroke patients for whom the benefits are judged to outweigh these risks.[4,10]

Most assessments of the treatment efficacy of IV rt-PA have arisen from randomized trials and have focused on short-term outcomes; to date, only 2 trials have reported outcomes at 12 months or later.[11,12] One study found that after 12 months of follow-up, patients treated with IV rt-PA within 3 hours after symptom onset had similar mortality to placebo patients but were more likely to have minimal or no disability.[11] The study by the third International Stroke Trial (IST-3) collaborative group reported that IV rt-PA was associated with significant improvements in functional outcomes, but not with reduced risk of mortality, after 18 months of follow-up.[12] Additionally, while several studies have reported short- and long-term outcomes among patients treated with IV rt-PA in real-world settings,[13-15] only 1 study has compared long-term outcomes between patients treated with or without IV rt-PA.[16] To add to this limited evidence base, we conducted a retrospective chart review study comparing mortality, hospital readmission, and long-term functional outcomes between patients who experienced ischemic stroke and were treated with IV rt-PA versus patients who were not treated with IV rt-PA.

Methods

Data Source

We conducted a retrospective chart review among neurologists in the United States who were actively treating patients who had experienced acute ischemic stroke. Neurologists were recruited through a large and nationally representative physician database. In order to be included in this database, physicians' credentials had to be verified against sources such as the American Medical Association database and through manual means such as verification of medical certificates and licenses. Neurologists who agreed to participate were asked to review the study inclusion and exclusion criteria and randomly select eligible acute ischemic stroke patients under their care who had received IV rt-PA and eligible patients who had not (non–rt-PA). A standardized chart abstraction form developed by the investigators was used by the neurologists to extract relevant information from the charts of selected patients. Abstracted patient data were anonymous and nonidentifiable; this study received an exemption from the New England Institutional Review Board on November 24, 2015.

Case Selection and Study Population

Adult patients having at least 1 inpatient admission for acute ischemic stroke recorded in their charts in 2013 or 2014 and no contraindications to IV rt-PA were eligible for inclusion. The first eligible acute ischemic stroke admission recorded in the chart was defined as the index stroke admission. Additional criteria for inclusion were (1) the patient's stroke severity, measured by the National Institutes of Health Stroke Scale[17] (NIHSS), was recorded at the index stroke admission before any treatment was administered; (2) the patient's medical chart was available for review from the time of the index stroke admission until his or her most recent follow-up visit or death; and (3) if the patient was alive at the time of chart abstraction, he or she was followed up for at least a year after the index stroke admission, or if the patient was deceased at the time of chart abstraction, a date of death was available in his or her charts.

Eligible patients were randomly selected and classified into either the IV rt-PA cohort or the non–rt-PA cohort based on the treatment during the index stroke admission. Randomization was performed with the use of a computerized random number generator. To ensure that the pretreatment stroke severity was similar between groups, NIHSS scores were classified into categories corresponding to different levels of 30-day mortality risk,[18] and randomization was stratified by the NIHSS mortality risk category.

Each physician could contribute a maximum of 6 patients (3 IV rt-PA patients and 3 non–rt-PA patients). Physicians were asked to verify and confirm the eligibility of the randomly selected patients before chart abstraction.

Covariates

Information on key covariates was abstracted from patients' charts. In particular, physicians abstracted available data on patient demographics (age, gender, race), patient history and comorbidities (hypertension, atrial fibrillation, coronary artery disease/prior myocardial infarction, carotid stenosis, diabetes mellitus, smoking status, and prior stroke admissions), and relevant details on the index stroke admission (treatments received, mode of transport to hospital, time between symptom onset and arrival, time between hospital arrival and neuroimaging, time between hospital arrival and administration of IV rt-PA, and admission unit).

Study Outcomes

The outcome data collected were based on information from follow-up visits documented in patients' charts. The primary outcomes assessed were mortality, time to hospital readmission, and time to independence. Mortality was defined as the time from the index stroke admission to death from any cause, time to hospital readmission was defined as the time from the index stroke admission to hospital readmission due to any cause, and time to independence was defined as the time from the index stroke admission to the first follow-up visit with a modified Rankin Scale[19,20] (mRS) score of 2 or lower.

Statistical Analysis

Patient baseline characteristics were summarized and compared using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Mortality, time to hospital readmission, and time to independence were described using Kaplan–Meier curves and compared using log-rank tests. Multivariate Cox proportional hazards regression models were applied to adjust for key patient characteristics; results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The following covariates were included in all multivariate Cox models: sex, age, race, pretreatment NIHSS score, hospital unit first admitted to, smoking status, atrial fibrillation, coronary artery disease or prior myocardial infarction, and number of prior stroke admissions. Patients with missing data on outcomes and covariates were excluded from the analyses. The proportional hazards assumption was assessed by testing the significance of a product term between IV rt-PA use and time added to the model. Statistical significance was defined as $P < .05$. All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

A total of 1026 charts were reviewed by 203 physicians. Participating physicians practiced in various settings: 32% in group practice, 28.1% in private practice, 22.7% at academic institutions, and 17.2% in hospitals (Appendix Table S1). The median time in practice was 13 years; 85.2% of the physicians practiced in urban locations, and 17.2% practiced in "stroke belt" states.[21]

Patient characteristics can be viewed in Table 1 and Appendix Table S2. The IV rt-PA group and the non–rt-PA group each contained 513 patients, with a median follow-up time of 15.7 months and 15.2 months, respectively. Compared with the non–rt-PA group, the IV rt-PA group was slightly younger and had a larger proportion of males. Patients' pretreatment stroke severity was similar between the groups (mean NIHSS scores: IV rt-PA = 11.7; non–rt-PA = 11.3; $P = .165$).

More IV rt-PA patients were first admitted to an intensive care unit during the index stroke admission (IV rt-PA = 57.1%; non–rt-PA = 19.5%; $P < .001$) (Table 1). In general, IV rt-PA patients were significantly more likely to have arrived at the hospital soon after symptom onset; 78.9% of all patients arrived within 4 hours, including 99.3% of IV rt-PA patients and 58.3% of non–rt-PA patients (Appendix Table S2).

Fewer IV rt-PA patients had records of atrial fibrillation (IV rt-PA = 20.9%; non–rt-PA = 31.8%; $P < .001$) or coronary artery disease or prior myocardial infarction (IV rt-PA = 30.2%; non–rt-PA = 36.6%; $P = .029$) in their charts. Fewer IV rt-PA patients never smoked (IV rt-PA = 24.6%; non–rt-PA = 32.7%; $P = .004$), and the average number of prior stroke admissions was greater among non–rt-PA patients (IV rt-PA = .2; non–rt-PA = .4; $P = .042$) (Table 1).

Log-rank tests comparing the Kaplan–Meier curves between groups showed that IV rt-PA patients experienced significantly better survival ($P = .013$), delayed hospital readmission ($P = .012$), and shorter time to independence ($P < .001$) compared with non–rt-PA patients (Fig 1).

HRs for IV rt-PA relative to non–rt-PA from multivariate Cox models are described in Table 2. Full model results can be viewed in Appendix Tables S3, S4, and S5. Compared with non-rt-PA patients, IV rt-PA patients had significantly lower mortality (HR [95% CI] = .52 [.30, .90]; $P = .02$), greater independence rates (HR [95% CI] = 1.42 [1.17, 1.71]; $P < .001$), and numerically lower hospital readmission rates (HR [95% CI] = .74 [.50, 1.08]). The proportional hazards assumption was satisfied in all analyses.

Discussion

In this large, real-world study of acute ischemic stroke patients treated by neurologists in different practice settings across the United States, we found that IV rt-PA patients had a significantly lower incidence of mortality

Table 1. *Patient characteristics*

Characteristics	Overall N = 1026		IV rt-PA N = 513		Non–rt-PA N = 513		*P* value
Demographics							
Sex, n (%)							
Male	619	(60.3%)	339	(66.1%)	280	(54.6%)	<.001†
Female	405	(39.5%)	172	(33.5%)	233	(45.4%)	<.001†
Unknown	2	(.2%)	2	(.4%)	0	(.0%)	.500
Age, median (range)	64.3	(21.0 - 98.7)	63.9	(21.0 - 92.7)	65.3	(23.2 - 98.7)	
Race							
White	573	(55.8%)	297	(57.9%)	276	(53.8%)	.187
Black	252	(24.6%)	130	(25.3%)	122	(23.8%)	.562
Hispanic	118	(11.5%)	55	(10.7%)	63	(12.3%)	.434
Asian	63	(6.1%)	22	(4.3%)	41	(8.0%)	.013*
Other	4	(.4%)	2	(.4%)	2	(.4%)	1.000
Unknown	16	(1.6%)	7	(1.4%)	9	(1.8%)	.614
Follow-up time (months), median (range)	15.5	(.0 - 35.6)	15.7	(.0 - 35.5)	15.2	(.1 - 35.6)	
Index stroke admission characteristics							
Pretreatment NIHSS, mean (SD)	11.5	(5.8)	11.7	(5.3)	11.3	(6.2)	.165
Pretreatment NIHSS category, n (%)							
Low: NIHSS 0-7	253	(24.7%)	123	(24.0%)	130	(25.3%)	.612
Medium: NIHSS 8-13	411	(40.1%)	206	(40.2%)	205	(40.0%)	.949
High: NIHSS 14-21	305	(29.7%)	155	(30.2%)	150	(29.2%)	.733
Very High: NIHSS 22-42	57	(5.6%)	29	(5.7%)	28	(5.5%)	.892
Hospital unit first admitted to, n (%)							
Stroke unit	536	(52.2%)	205	(40.0%)	331	(64.5%)	<.001†
Observation ward	27	(2.6%)	7	(1.4%)	20	(3.9%)	.011*
Intensive care unit	393	(38.3%)	293	(57.1%)	100	(19.5%)	<.001†
General ward	51	(5.0%)	2	(.4%)	49	(9.6%)	<.001†
Department of neurosurgery	3	(.3%)	0	(.0%)	3	(.6%)	.249
Other	7	(.7%)	3	(.6%)	4	(.8%)	1.000
Unknown	9	(.9%)	3	(.6%)	6	(1.2%)	.506
Comorbidities							
Smoking status, n (%)							
Current smoker	206	(20.1%)	112	(21.8%)	94	(18.3%)	.161
Former smoker	463	(45.1%)	248	(48.3%)	215	(41.9%)	.038*
Never smoker	294	(28.7%)	126	(24.6%)	168	(32.7%)	.004†
Unknown	63	(6.1%)	27	(5.3%)	36	(7.0%)	.242
Atrial fibrillation, n (%)							
Yes	270	(26.3%)	107	(20.9%)	163	(31.8%)	<.001†
No	732	(71.3%)	394	(76.8%)	338	(65.9%)	<.001†
Unknown	24	(2.3%)	12	(2.3%)	12	(2.3%)	1.000
Coronary artery disease/prior myocardial infarction, n (%)							
Yes	343	(33.4%)	155	(30.2%)	188	(36.6%)	.029*
No	667	(65.0%)	352	(68.6%)	315	(61.4%)	.015*
Unknown	16	(1.6%)	6	(1.2%)	10	(1.9%)	.314
Number of prior stroke admissions, mean (SD)	.3	(.9)	.2	(.7)	.4	(1.0)	.042*

Abbreviations: IV, intravenous; n, number; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation.

*$P < .05$.

†$P < .01$.

and better functional status compared with non rt-PA patients over a median follow-up time of 15.5 months.

To our knowledge, only one other study has compared long-term mortality between IV rt-PA and non–rt-PA patients in a real-world setting.[16] Schmitz et al conducted a cohort study using a nationwide stroke registry in Denmark and found that, compared with patients with acute ischemic stroke who were eligible for IV rt-PA but

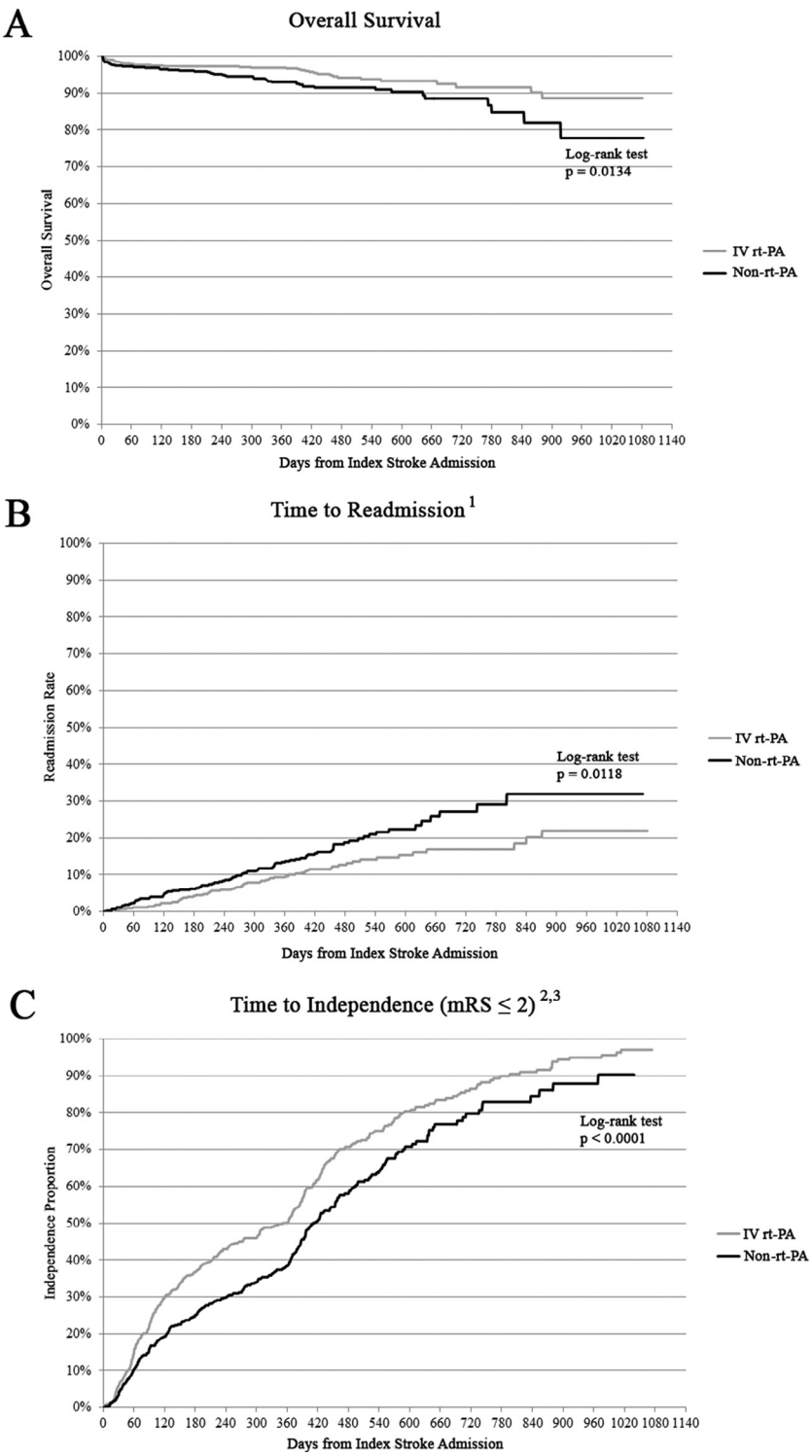

Figure 1. *Kaplan–Meier curves of (A) mortality, (B) time to hospital readmission, and (C) time to independence in IV rt-PA and non-rt-PA patients. Abbreviations: IV, intravenous; mRS, modified Rankin Scale; rt-PA, recombinant tissue plasminogen activator.*
Notes:
1. 166 patients were excluded from the time to first hospital readmission analysis due to unknown readmission status or date of hospital readmission.
2. 127 patients were excluded from the time to independence analysis due to missing mRS scores.
3. mRS ranges from 0 to 6, where 0 = no symptoms, 1 = no significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, 6 = dead.

did not receive it, patients treated with IV rt-PA experienced lower long-term mortality over a median of 1.4 years of follow-up (HR [95% CI] = .66 [.49, .88]).[16]

Randomized trials have generally indicated no overall survival benefit of IV rt-PA during either short-term (3 months in most trials)[7] or long-term follow-up (12 or 18 months).[12] However, while overall mortality at the end of the trial follow-up appears comparable between IV rt-PA patients and controls, pooled estimates from several trials indicate that mortality *after* the first 7-10 days is significantly lower for patients treated with IV rt-PA than for controls,[7] suggesting that patients treated with IV rt-PA who survive the initial risks associated with the treatment have lower subsequent mortality

Table 2. *Comparison of mortality, independence, and hospital readmission between IV rt-PA and non–rt-PA patients*

	Unadjusted		Adjusted	
Outcomes	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Death[1]	.56 (.35-.90)	.016*	.52 (.30-.90)	.020*
Independence (mRS ≤ 2)[2]	1.42 (1.21-1.66)	<.001†	1.42 (1.17-1.71)	<.001†
Hospital readmission[3]	.65 (.46-.91)	.011*	.74 (.50-1.08)	.121

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale.
Notes:
1. 39 patients were excluded due to missing covariates.
2. 162 patients were excluded due to missing mRS scores (n = 127) or covariates (n = 35).
3. 180 patients were excluded due to missing information regarding hospital readmissions (n = 166) or covariates (n = 39).
*$P < .05$.
†$P < .01$.

than patients who remain untreated. The benefits seen here and in Schmitz et al's study may reflect improvements in the identification of patients who can be safely treated with IV rt-PA as experience with treatment guidelines increases.[22]

It should be noted that our Kaplan–Meier estimates of 12-month overall mortality (3% and 7% in the IV rt-PA and non–rt-PA groups, respectively) are substantially lower than estimates reported over similar time frames in other studies.[11,13,16,23] The estimated mortality of the IV rt-PA group in Schmitz et al was approximately 10% by 12 months.[16] Other clinical studies including only patients treated with IV rt-PA have estimated 12-month mortality to be between 15% and 25%,[13,23] while reported 12-month mortality in the NINDS trial was approximately 24% for IV rt-PA patients and 28% for controls.[11]

A potential explanation for the lower mortality observed in our study is that, despite our request to randomly select patient charts, physicians in the study may have preferentially selected living patients, leading to an underestimation of mortality among both patient groups. The requirement of the death date might have led to the exclusion of some diseased patients and contributed to the potential underestimation of mortality as well. Our estimate of the inverse association between IV rt-PA treatment and mortality may be overstated if deceased patients whose charts were not included were more likely to be in the IV rt-PA group rather than the non–rt-PA group. IV rt-PA patients selected for inclusion may therefore be more reflective of IV rt-PA patients who survive beyond the early risk period rather than the entire population of patients treated with IV rt-PA. However, given the observed adjusted HR of .52 (95% CI, .30, .90) for mortality, it appears unlikely that a large enough disparity in the likelihood of exclusion would exist between the groups to entirely eliminate this observed inverse association. Additionally, the validity of our estimate is supported by the observation of a comparable effect size in Schmitz et al's study,[16] which would not have had the same limitation.

Similar to mortality, prior comparisons of longitudinal changes in functional status between IV rt-PA patients and non–rt-PA patients have only been reported in randomized trials, with a greater proportion of patients treated with IV rt-PA noted to be alive and independent at the end of follow-up.[24] Our Kaplan–Meier estimates of independence (mRS ≤ 2) by 12 months of 52% and 39% among IV rt-PA and non–rt-PA patients, respectively, are comparable with other studies. A clinical study of patients treated with IV rt-PA reporting mRS scores at 12 months indicated that 52% of the patients had scores of 0-2 after 1 year of follow-up.[23] A meta-analysis of IV rt-PA clinical trials observed that the proportions of patients treated with IV rt-PA and controls with mRS scores of 0-2 by the end of follow-up (1-6 months) were 46% and 42%, respectively.[24] Overall, our finding that patients treated with IV rt-PA had a better functional status than non–rt-PA patients is consistent with randomized clinical trial findings.[7]

Hospital readmission rates for the IV rt-PA group were numerically lower than, but not significantly different from, the rates for the non–rt-PA group. To our knowledge, no studies have examined whether readmission rates are lower in IV rt-PA patients. However, in two studies, thrombolysis in general was not associated with readmission over either a 1-month[25] or a 1-year[26] follow-up period. Future studies might investigate this research question due to the substantial impact of hospital readmission on patients' resource utilization and costs.

This study's findings have several important implications. For patients, better poststroke functional status has previously been associated with longer survival[27] and higher quality of life.[28] In terms of cost-effectiveness, despite the high short-term costs of IV rt-PA use,[29] several studies have concluded that IV rt-PA treatment is a cost-effective intervention in the long term, given the potential cost-savings associated with reduced long-term morbidity and mortality.[30,31] A recent administrative claims analysis estimated that over half of the total yearly health-care costs

associated with acute ischemic stroke in the United States result from inpatient, outpatient, emergency room, or pharmacy visits between 31 and 365 days after the initial stroke admission.[32] A separate analysis indicated that acute ischemic stroke patients discharged with disability had substantially higher costs during the 1-year period postdischarge than patients discharged without disability.[33] Consequently, the use of IV rt-PA in eligible patients to improve long-term functional status and reduce mortality could potentially reduce long-term health-care costs.

At present, IV rt-PA treatment for acute ischemic stroke is approved by the Food and Drug Administration for use only within 3 hours of symptom onset.[34] While current American Heart Association/American Stroke Association guidelines endorse the use of IV rt-PA in a limited subset of patients up to 4.5 hours of symptom onset,[4,10] the balance of risks and benefits of IV rt-PA treatment beyond 3 hours remains a matter of debate.[9] In our study of patients without contraindications for IV rt-PA use, 87% of patients receiving IV rt-PA were treated within less than 3 hours, suggesting that our results are largely applicable to patients eligible for IV rt-PA who are treated within this 3-hour time frame.

Future studies might examine whether the benefits observed in this study remain in subgroups of patients, such as those who arrive after more than 3 hours, and whether diminishing returns in benefit are noted as the treatment delay increases. Future studies could also investigate whether the association between IV rt-PA treatment and improved survival or functional status varies depending on NIHSS score, age, or comorbidities. Such knowledge could help further target IV rt-PA use and maximize the likelihood of benefit for individual patients.

This study is subject to common limitations of a chart abstraction approach to data collection. Namely, data quality is dependent on the accuracy and completeness of the chart documentation and on the abstraction by the neurologists. Mortality and readmission were both captured to the extent available in the charts; the occurrence of these events outside of the physician's hospital network might not have been captured. For a proportion of patients, mRS scores were not directly recorded in the chart; in these instances, physicians were asked to estimate mRS scores based on the available information in the chart. Finally, despite adjustment for important confounders like stroke severity and age, residual confounding may remain given the observational nature of this study.

Conclusion

This study adds to the limited evidence base on long-term outcomes of acute ischemic stroke patients treated with IV rt-PA. It indicates long-term clinical benefits of IV rt-PA in survival and functional status for acute ischemic stroke patients.

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Appendix: Supplementary Material

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