ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Beneficial effects of the 30-minute door-to-needle time standard for alteplase administration

Suja S. Rajan[1,2], Marquita Decker-Palmer[3], Jessica Wise[1], Thanh Dao[4], Cindy Salem[3] & Sean I. Savitz[2,4,5]

[1]Department of Management, Policy and Community Health, School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas
[2]Institute for Stroke and Cerebrovascular Disease, The University of Texas Health Science Center at Houston, Houston, Texas
[3]Genentech, Inc., South San Francisco, California
[4]Memorial Hermann Health System, Houston, Texas
[5]Department of Neurology, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, Texas

Correspondence
Suja S. Rajan, Department of Management, Policy and Community Health, School of Public Health, The University of Texas Health Science Center at Houston, Rm E1015, 1200 Pressler St, Houston, TX 77030. Tel: +1 713 500 9194; Fax: +1 713 500 9493; E-mail: suja.s.rajan@uth.tmc.edu

Funding Information
This manuscript was sponsored by F. Hoffmann-La Roche Ltd./Genentech, Inc.

Received: 16 March 2021; Revised: 29 April 2021; Accepted: 17 May 2021

Annals of Clinical and Translational Neurology **2021; 8(8): 1592–1600**

doi: 10.1002/acn3.51400

Abstract

Objective: The American Heart Association recently raised the bar on the timely treatment of acute ischemic stroke (AIS) with intravenous alteplase. Our study looks at the effectiveness of this new standard, by examining the effect of varying door-to-needle times of alteplase initiation on the clinical, quality of care, and efficiency of care outcomes. **Methods**: This retrospective case–control study examined 752 AIS patients treated with intravenous alteplase in a large academic health system during 2015–2018, and compared their outcomes after treatment within 30, 45, and 60 min of arrival. The outcomes compared were: (1) clinical – discharge and 90-day modified Rankin Scale (mRS), and post-intravenous alteplase (24-h) NIH Stroke Scale (NIHSS); (2) quality of care – inpatient mortality, 30-day readmission, discharge to home, and disability at discharge; (3) efficiency of care – length of stay (LOS) and index stroke hospitalization costs. Adjusted logistic and linear regression analyses were used to estimate the effects, after controlling for baseline characteristics. **Results**: Based on the adjusted regression analyses, treatment within 30 min of arrival was associated with better post-treatment mRS and NIHSS scores, and the clinical benefits were reduced when the windows were expanded to within 45 or 60 min. An important finding of the study was that treatment within 30 min of arrival significantly reduced the average LOS. **Interpretation**: Early intravenous alteplase treatment significantly improved clinical and efficiency of care outcomes. This study provides evidence that meeting the new AHA *Target Stroke* recommendations will help hospitals improve patient clinical outcomes and reduce LOS, thereby improving the efficiency of care standards.

Introduction

Stroke is the leading cause of long-term disability in the United States and across the world.[1,2] Moreover, stroke is the second leading cause of death in the world and the fifth leading cause of death in the United States.[1,2] In addition to the disease burden, stroke is among the 15 most expensive conditions treated in U.S. hospitals and one of the 10 most expensive conditions billed to Medicare.[3] The incidence, prevalence, and total cost burden of stroke will continue to increase as the U.S. population ages. Projections indicate that by 2030, approximately 4% of the U.S. population will have had a stroke event and the healthcare spending will be almost $200 billion (2010 $), a 250% increase in comparison to medical costs in 2012.[4]

Acute ischemic stroke (AIS) accounts for 87% of all stroke events.[1] Standard of care in AIS treatment includes the administration of intravenous (IV) alteplase within 0 to 4.5 h of symptom-onset, to ensure cerebral reperfusion, for eligible patients.[5–7] Administration of IV alteplase, and especially timely initiation of IV alteplase, is

critical for better short-term and long-term health outcomes among AIS patients.[8–11]

Since timely delivery of IV alteplase is critical for health outcomes and cost burden after AIS, time to initiation of IV alteplase has become increasingly important for ensuring high quality, effective, and efficient stroke management. Although AIS symptom-onset to IV alteplase initiation time is the direct measure of timely treatment, this time is often not in the control of providers, and is many times difficult to measure due to its dependence on patient/caregiver observation and reporting of the actual symptom-onset. Consequently, hospital arrival to alteplase initiation time (hereafter referred to as door-to-needle time) is also used and emphasized by providers, healthcare systems, clinical guidelines, and national quality initiatives as a measure of AIS quality of care.

In line with improving this quality of care measure, the American Heart Association (AHA) launched its *Target: Stroke* initiative in 2010, with the primary goal of assisting hospitals to streamline their caregiving processes to reduce door-to-needle times for AIS.[12] Following the continued success of *Target: Stroke* during the past decade, with a substantial number of hospitals achieving the door-to-needle time goals set by this initiative, the Phase III of this initiative was rolled out in 2019.[12] In Phase III, AHA further raised the bar on the timely treatment of AIS with IV alteplase. AHA recommended door-to-needle times of 30 min or less for 50% or more of the eligible AIS patients, in addition to the goals of 60 min or less door-to-needle times for 85% or more of the eligible AIS patients, and 45 min or less door-to-needle times for 75% or more of the eligible AIS patients.

In spite of the use and importance of the door-to-needle time as a quality of care measure, previous studies in the literature have predominantly evaluated the effectiveness of symptom-onset to IV alteplase initiation time.[13–16] The two studies, to our knowledge, that examine the effectiveness of the door-to-needle time have only looked at in-hospital and 1-year all-cause mortality, and all-cause readmissions.[17,18] There is a dearth of studies that particularly focus on the new 30-min door-to-needle time threshold. This study aimed to address this gap by providing evidence supporting the *Phase III Target: Stroke* initiative, and examining the effectiveness of door-to-needle times within 30, 45, and 60 min on a range of outcomes including: (1) clinical outcomes; (2) quality of care outcomes; and (3) efficiency of care outcomes.

Methods

Study design and data sources

This study is a retrospective case–control study involving secondary data analysis of patients 18 years and older, with an acute onset of ischemic stroke between June 1st, 2015 and July 31st, 2018, who were admitted to the Memorial Hermann Health System (MHHS) in the Greater Houston Area. The study used three data sources: (1) The MHHS-University of Texas Health Science Center at Houston's stroke registry which includes all stroke incident cases admitted to MHHS; (2) the electronic medical record (EMR) data from the MHHS; and (3) MHHS's financial/billing data.

Patient information such as arrival date and time, IV alteplase bolus initiation date and time, admission and discharge dates, date of birth, gender, race–ethnicity, presence of comorbidities, National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scores (mRS), discharge dispositions, and inpatient mortality were obtained from the stroke registry. MHHS financial/billing data provided information on 30-day readmissions, patient insurance, specialty of the admitting physician, and cost of the hospital stay associated with the index stroke. In addition, the MHHS financial/billing data provided supplemental information on admission and discharge dates, date of birth, gender, race–ethnicity, discharge dispositions, and inpatient mortality. The presence of comorbidities was obtained both from the information present in the stroke registry and the International Classification of Diseases 9 and 10 information in the MHHS financial/billing data. If information in variables present in both the stroke registry and the MHHS financial/billing data had discrepancies for the same patient, an EMR review was performed to validate and establish the correct information. Furthermore, EMR reviews were also performed to obtain missing information in the stroke registry for variables such as arrival date and time, IV alteplase bolus initiation date and time, race–ethnicity, NIHSS, and mRS.

The study was limited to patients who received IV alteplase in MHHS within 180 min of hospital arrival (door-to-needle time). Inpatient MHHS patients who had an AIS incidence during a hospital stay were excluded as door-to-needle time computations are not relevant for this sub-group. In addition, patients who were administered IV alteplase in another hospital/health system, and were transferred to MHHS for further management or endovascular therapy, were excluded as their door-to-needle time was not present in the study data. Patients who were administered IV alteplase in MHHS's Mobile Stroke Unit were excluded as door-to-needle time was negative and not relevant for this sub-group. Six patients had more than one stroke event during the study period, hence only their first stroke event was retained in the study sample to avoid repeat sampling issues, which would be challenging to statistically account for with a repeat sample size of six patients.

Dependent variables

Three groups of outcome measures were evaluated:

1 Clinical outcomes: Three outcome variables were evaluated in this category. The first was a binary variable capturing *mRS at discharge* (coded as 1 when mRS >2, and 0 when mRS is ≤2). The second was a binary variable capturing *mRS at 90 days* (coded as 1 when mRS >2, and 0 when mRS is ≤2). The third was a binary variable capturing *post-IV alteplase NIHSS* (coded as 1 when NIHSS >5, and 0 when NIHSS is ≤5), which was NIHSS measured at 24 h after IV alteplase administration. Patients who died during the hospital stay (n = 57) were classified as mRS "6" for both mRS at discharge and mRS at 90 days. mRS at discharge was "6" only for these 57 patients who died during the hospital stay. Fifty-eight additional patients died at or before 90 days, so 115 patients had an mRS of "6" at 90 days.
2 Quality of care outcomes: Four outcome variables were evaluated in this category. The first was a binary variable capturing *inpatient mortality* (yes/no). The second was a binary variable capturing *30-day readmission* (yes/no). The third was a binary variable capturing *discharge to home* (yes/no). The fourth was a binary variable capturing *disability at discharge* (yes/no). Discharge disposition was used to create the *disability at discharge* variable. Based on methods used in the literature, disability at discharge was defined as discharge to any short-term, intermediate care, or long-term inpatient facility including inpatient rehabilitation.[19] Patients who died during the hospital stay were excluded from the analysis of 30-day readmission and disability at discharge. Patients who died during the hospital stay were not excluded from the analysis of "discharge to home."
3 Efficiency of care outcomes: Two outcome variables were evaluated in this category. The first was the *length of stay (LOS)*, a continuous variable measured in days. The second was *index stroke hospitalization cost*, a continuous variable measured in dollars.

Independent variables

The three independent variables of interest were binary variables indicating: (1) whether or not a patient had 30 min or less door-to-needle time (coded as 1 if the door-to-needle time was 0–30 min and 0 if the door-to-needle time was 31–180 min); (2) whether or not a patient had 45 min or less door-to-needle time (coded as 1 if the door-to-needle time was 0–45 min and 0 if the door-to-needle time was 46–180 min); and (3) whether or not a patient had 60 min or less door-to-needle time (coded as 1 if the door-to-needle time was 0–60 min and 0 if the door-to-needle time was 61–180 min).

Other independent variables adjusted for in the regressions included patient sociodemographic and patient clinical characteristics, and other characteristics. Patient sociodemographic characteristics adjusted for were age at stroke incidence (continuous variable in years), gender (binary variable capturing male/female), race–ethnicity (four-category variable capturing non-Hispanic white, non-Hispanic black, Hispanic, and non-Hispanic other), and insurance at stroke incidence (binary variable capturing Medicare/non-Medicare). Insurance was initially categorized as a four-category variable (Private, Medicare, Medicaid, and Other) but later converted to a binary variable based on the sample size of each category and statistical significance tests during the regression model building. Patient baseline clinical characteristics adjusted for were baseline NIHSS (continuous variable), binary variables capturing the presence of comorbidities such as diabetes mellitus, cardiovascular disease, obesity, chronic obstructive pulmonary disease, and chronic kidney disease, and binary variable capturing whether or not a patient was a smoker. Other characteristics adjusted for were the specialty of admitting physicians (binary variable capturing Neurologist-Neuro Surgeon/Other), and year of stroke incidence (four-category variable with categories - 2015, 2016, 2017, and 2018).

Statistical analysis

Independent and dependent variables were examined for each group of door-to-needle categories, and t tests were used to test the differences in descriptive statistics (Tables 1 and 2). LOS and index stroke hospitalization costs were the only two continuous dependent variables. Based on the distribution of these two variables and specification tests, generalized linear model was used for the adjusted regression analyses of these continuous variables (Table 3).[20] All other dependent variables were analyzed using logistic regression (Table 3). For the continuous independent variables, higher order terms were tested and square of age at stroke incidence was included in the regressions based on statistical significance and model fit.

Results

A total of 752 patients were included in the study based on the inclusion–exclusion criteria outlined in the study design section. Descriptive statistics for most independent variables were statistically different for 0–45 min versus 46–180 min door-to-needle time categories (Table 1). Comparing these two categories revealed that on average patients treated early (in 0–45 min) were more likely to be younger, male, non-Hispanic white, privately insured and a smoker, and less likely to be non-Hispanic black, be Medicare insured, and

Table 1. Descriptive statistics for the patient sociodemographic, patient clinical, and other characteristics by door-to-needle time categories.

	Door-to-needle time categories					
	0–30 min (*n* = 138)	31–180 min (*n* = 614)	0–45 min (*n* = 356)	46–180 min (*n* = 396)	0–60 min (*n* = 550)	61–180 min (*n* = 202)
Patient sociodemographic characteristics						
Age at stroke incidence, y	66.35 (1.31)	67.33 (0.61)	65.60* (0.75)	68.54* (0.78)	66.64 (0.61)	68.53 (1.14)
Gender						
Female	42.03 (4.22)	48.37 (2.02)	42.42* (2.62)	51.52* (2.51)	46.18 (2.13)	50.00 (3.53)
Male	57.97 (4.22)	51.63 (2.02)	57.58* (2.62)	48.48* (2.51)	53.82 (2.13)	50.00 (3.53)
Race–ethnicity						
Non-Hispanic White	50.00* (4.27)	39.90* (1.98)	46.35* (2.65)	37.63* (2.44)	42.55 (2.11)	39.60 (3.45)
Non-Hispanic Black	28.26 (3.85)	33.55 (1.91)	29.21** (2.41)	35.61** (2.41)	30.91 (1.97)	37.13 (3.41)
Hispanic	13.77 (2.94)	17.92 (1.55)	16.01 (1.95)	18.18 (1.94)	17.45 (1.62)	16.34 (2.61)
Other	7.97 (2.31)	8.63 (1.13)	8.43 (1.47)	8.59 (1.41)	9.09 (1.23)	6.93 (1.79)
Insurance at stroke incidence						
Private	31.88* (3.98)	22.31* (1.68)	28.93* (2.41)	19.70* (2.00)	25.45 (1.86)	20.30 (2.84)
Medicare	51.45 (4.27)	56.68 (2.00)	50.84* (2.65)	60.10* (2.46)	53.82** (2.13)	60.89** (3.44)
Medicaid	7.97 (2.31)	10.91 (1.26)	8.99 (1.52)	11.62 (1.61)	9.82 (1.27)	11.88 (2.28)
Other	8.70 (2.41)	10.10 (1.22)	11.24 (1.68)	8.59 (1.41)	10.91 (1.33)	6.93 (1.79)
Patient baseline clinical characteristics						
Baseline NIH stroke scale	12.36 (0.60)	12.27 (0.33)	12.67 (0.41)	11.94 (0.42)	12.66* (0.34)	11.27* (0.59)
Presence of diabetes mellitus	31.88** (3.98)	39.90** (1.98)	34.83* (2.53)	41.67* (2.48)	36.00* (2.05)	45.05* (3.51)
Presence of cardiovascular disease	65.22 (4.07)	68.40 (1.88)	65.45 (2.52)	69.95 (2.31)	66.36 (2.02)	71.78 (3.17)
Presence of obesity	13.04 (2.88)	12.05 (1.31)	13.48 (1.81)	11.11 (1.58)	13.45** (1.45)	8.91** (2.01)
Presence of chronic obstructive pulmonary disease	4.35 (1.74)	7.33 (1.05)	4.78* (1.13)	8.59* (1.41)	5.09* (0.93)	11.39* (2.24)
Presence of chronic kidney disease	15.94* (3.13)	24.10* (1.73)	19.66** (2.11)	25.25** (2.19)	22.36 (1.78)	23.27 (2.98)
Being a smoker	32.61 (4.01)	30.29 (1.86)	33.71** (2.51)	28.03** (2.26)	30.73 (1.97)	30.69 (3.25)
Other characteristics						
Specialty of admitting physician						
Neurologist/Neuro-Surgeon	44.93* (4.25)	59.28* (1.98)	54.78 (2.64)	58.33 (2.48)	56.36 (2.12)	57.43 (3.49)
Other	55.07* (4.25)	40.72* (1.98)	45.22 (2.64)	41.67 (2.48)	43.64 (2.12)	42.57 (3.49)
Year of stroke						
2015	7.97** (2.31)	13.68** (1.39)	10.11* (1.60)	14.90* (1.79)	10.73* (1.32)	17.82* (2.70)
2016	13.04* (2.88)	25.08* (1.75)	17.42* (2.01)	27.78* (2.25)	20.00* (1.71)	30.69* (3.25)
2017	39.13 (4.17)	35.34 (1.93)	38.76 (2.59)	33.59 (2.38)	38.91* (2.08)	28.22* (3.17)
2018	39.86* (4.18)	25.90* (1.77)	33.71* (2.51)	23.74* (2.14)	30.36** (1.96)	23.27** (2.98)

Unless specified otherwise, all numbers are percentages with standard errors in parentheses.
*$p \leq 0.05$.
**$p \leq 0.10$.

have comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease, as compared with patients treated later (in 46–180 min). As expected, with each passing year the likelihood of being treated early increased, similar to the national trends in response to the *Target: Stroke* initiative. Fewer independent variables were statistically different between the other door-to-needle time categories, with 30 and 60-min thresholds. The independent variables that were statistically different were mostly in the same direction as the 45-min door-to-needle time threshold categories.

Based on the bivariate analysis (Table 2) door-to-needle time of 30 min or less significantly reduced LOS, and improved all the clinical outcomes namely – the mRS at discharge and 90 days, and post-IV alteplase NIHSS. Door-to-needle time of 45 min or less, and 60 min or less, improved the mRS at discharge and 90 days, and reduced inpatient mortality.

Adjusted regression analysis showed similar results (Table 3). Door-to-needle time of 30 min or less significantly reduced LOS, and improved all the clinical outcomes namely - the mRS at discharge and 90 days, and post-IV alteplase NIHSS. The adjusted difference in LOS was about 1.5 days lower for patients treated within 30 min of arrival versus those treated between 31 and 180 min. Door-to-needle time of 30 min or less did not have any effect on the quality of care outcomes. Door-to-needle time of 45 min or less improved mRS at discharge

Table 2. Descriptive statistics for the dependent variables by door-to-needle time categories.

	Door-to-needle time categories					
	0–30 min (n = 138)	31–180 min (n = 614)	0–45 min (n = 356)	46–180 min (n = 396)	0–60 min (n = 550)	61–180 min (n = 202)
Clinical outcomes associated with timely IV alteplase administration						
Modified Rankin Score at discharge						
≤2	41.00* (4.94)	27.64* (1.93)	35.79* (2.84)	24.86* (2.30)	31.95** (2.18)	24.18** (3.18)
>2	59.00* (4.94)	72.36* (1.93)	64.21* (2.84)	75.14* (2.30)	68.05** (2.18)	75.82** (3.18)
Modified Rankin Score at 90 days						
≤2	59.57* (5.09)	45.53* (2.27)	53.03* (3.08)	43.41* (2.82)	50.23* (2.42)	40.82* (4.07)
>2	40.43* (5.09)	54.47* (2.27)	46.97* (3.08)	56.59* (2.82)	49.77* (2.42)	59.18* (4.07)
Post-IV alteplase NIH Stroke Scale						
≤5	61.31** (4.18)	52.61** (2.05)	56.03 (2.66)	52.62 (2.56)	55.06 (2.15)	52.04 (3.58)
>5	38.69** (4.18)	47.39** (2.05)	43.97 (2.66)	47.38 (2.56)	44.94 (2.15)	47.96 (3.58)
Quality-of-care outcomes associated with timely IV alteplase administration						
Inpatient mortality						
Yes	6.52 (2.11)	7.82 (1.08)	5.90** (1.25)	9.09** (1.45)	5.45* (0.97)	13.37* (2.40)
No	93.48 (2.11)	92.18 (1.08)	94.10** (1.25)	90.91** (1.45)	94.55* (0.97)	86.63* (2.40)
30-day readmission						
Yes	8.53 (2.47)	9.89 (1.26)	8.36 (1.51)	10.83 (1.64)	9.81 (1.31)	9.14 (2.18)
No	91.47 (2.47)	90.11 (1.26)	91.64 (1.51)	89.17 (1.64)	90.19 (1.31)	90.86 (2.18)
Discharge to home						
Yes	53.62 (4.26)	48.37 (2.02)	51.40 (2.65)	47.47 (2.51)	51.09 (2.13)	44.55 (3.51)
No	46.38 (4.26)	51.63 (2.02)	48.60 (2.65)	52.53 (2.51)	48.91 (2.13)	55.44 (3.51)
Disability at discharge						
Yes	42.64 (4.37)	47.53 (2.10)	45.37 (2.72)	47.78 (2.64)	45.96 (2.19)	48.57 (3.79)
No	57.36 (4.37)	52.47 (2.10)	54.63 (2.72)	52.22 (2.64)	54.04 (2.19)	51.43 (3.79)
Efficiency-of-care outcome associated with timely IV alteplase administration						
Length of stay, d	5.04* (0.31)	6.59* (0.27)	5.92 (0.30)	6.65 (0.33)	6.22 (0.26)	6.53 (0.44)
Index stroke hospitalization cost, USD	35,724.45 (1461.86)	35,623.43 (1028.43)	36,077.31 (1179.82)	35,250.60 (1295.31)	36,370.38 (1008.23)	33,658.69 (1792.56)

Abbreviations: IV, intravenous; NIH, National Institutes of Health; USD, US dollars.

Unless specified otherwise, all numbers are percentages with standard errors in parentheses.

*$p \leq 0.05$.

**$p \leq 0.10$.

Table 3. Effect of timely IV alteplase administration on clinical, quality-of-care, and efficiency-of-care outcomes.

	Patients treated with IV alteplase within 0–30 min versus 31–180 min of arrival	Patients treated with IV alteplase within 0–45 min versus 46–180 min of arrival	Patients treated with IV alteplase within 0–60 min versus 61–180 min of arrival
Clinical outcomes associated with timely IV alteplase administration			
1. Modified Rankin Score at discharge[1]	0.45* (0.26 to 0.78)	0.62* (0.41 to 0.96)	0.70 (0.43 to 1.15)
2. Modified Rankin Score at 90 days[1]	0.58* (0.36 to 0.96)	0.68* (0.47 to 0.99)	0.51* (0.33 to 0.79)
3. Post-IV alteplase NIH Stroke Scale[1]	0.56* (0.35 to 0.91)	0.84 (0.57 to 1.23)	0.82 (0.53 to 1.26)
Quality-of-care outcomes associated with timely IV alteplase administration			
1. Inpatient mortality[1]	1.05 (0.47 to 2.35)	0.64 (0.34 to 1.20)	0.25* (0.13 to 0.49)
2. 30-day readmission[1]	0.91 (0.45 to 1.85)	0.76 (0.44 to 1.31)	1.10 (0.58 to 2.09)
3. Discharged home[1]	1.34 (0.87 to 2.07)	1.16 (0.82 to 1.65)	1.45* (1.00 to 2.16)
4. Disability at discharge[1]	0.75 (0.48 to 1.17)	0.86 (0.60 to 1.22)	0.76 (0.50 to 1.15)
Efficiency of care outcomes associated with timely IV alteplase administration			
1. Length of stay (GLM)[2]	–0.21* (–0.35 to –0.06)	–0.08 (–0.20 to 0.04)	–0.07 (–0.21 to 0.06)
2. Index stroke hospitalization cost[2]	0.02 (–0.08 to 0.13)	0.01 (–0.08 to 0.09)	0.02 (–0.08 to 0.11)

Abbreviations: GLM, generalized linear model; IV, intravenous; NIH, National Institutes of Health.
Confidence intervals in parentheses. The regressions were adjusted for baseline NIH Stroke Scale, patient sociodemographic characteristics, and clinical characteristics, as listed in Table 1.
[1]Odds ratios from logistic regressions.
[2]Coefficients from linear regressions.
*$p \leq 0.05$.

and 90 days. Door-to-needle time of 60 min or less improved the mRS at 90 days and improved the quality of care outcomes by reducing the odds of inpatient mortality and increasing the odds of discharge to home. The different door-to-needle time categories had no effect on 30-day readmissions, disability at discharge, and costs.

In the adjusted analyses, variables that were most consistently statistically associated with poor clinical outcomes were non-Hispanic Black and Hispanic race–ethnicity, and the presence of diabetes mellitus and obesity. Diabetes mellitus and obesity were also associated with lower likelihood of home discharge, higher likelihood of disability at discharge, and longer LOS.

In order to understand if the patients treated at the upper end of the door-to-needle time window drove the results, we performed a sensitivity analysis by excluding patients who were treated after 120 min (i.e., door-to-needle time >120). Twenty-eight out of the 752 patients were treated between 121 and 180 min. The magnitudes of the odds ratios stayed similar and the direction of the odds ratios stayed the same in these new regressions. The statistical significance of the odds ratios reduced for only two regressions (mRS at 90 days at the 45-min threshold and discharge to home at the 60-min threshold). However, given that the p values for these two odds ratios were still below 0.10, the directions of the odds ratios did not change, and the magnitudes changed by less than 3% points, it is highly likely that the drop in the statistical significance was due to the reduction in sample size. None of the regressions that illustrated the effectiveness of the 30-min door-to-needle threshold changed. This established the robustness of our results, especially at the 30-min threshold.

Discussion

This study showed that early IV alteplase treatment within 30 min of hospital arrival significantly improved clinical and efficiency of care outcomes. Clinical outcomes were mostly improved for all the lower door-to-needle time categories, and the magnitudes of improvement in these outcomes were higher for door-to-needle time within 30 min, as opposed to door-to-needle time within 45 or 60 min. Only patients with door-to-needle time within 30 min showed improvement in the efficacy of care outcome, in the form of improved LOS. However, quality of care outcomes did not improve beyond the 60-min door-to-needle threshold.

Reduction in LOS associated with early IV alteplase treatment is a significant finding of this study, which has not been examined by similar studies before. It is important to note, that in this study, a statistically significant reduction in LOS was associated with treatment within 30 min of arrival (as compared with treatment within 31–180 min of arrival), but not with the 45 and 60 min thresholds. LOS is the primary determinant of use of healthcare services and bed turnover, which in turn affect hospital profit margins. Therefore, LOS is a critical measure of efficiency of care for hospitals. Reduction in LOS reduces nosocomial infections and medication-related

adverse events, and reduces the burden of reimbursements and out-of-pocket payments for insurers and patients, respectively.[21–24] Reduced reimbursements and out-of-pocket costs ensure lower societal costs.[22–24] Given these benefits, there is considerable pressure on providers to reduce LOS. This study provides evidence that meeting the new AHA *Target Stroke* recommendations will help hospitals improve patient clinical outcomes and reduce LOS, thereby improving their efficiency of care standards.

The findings from our study demonstrating beneficial outcomes of lower door-to-needle times are similar to past studies examining any use of IV alteplase (vs. placebo), and examining benefits of lower symptom-onset to IV alteplase administration times. Previous studies have demonstrated that early use of IV alteplase in AIS is clinically efficacious as well as cost-effective.[13–18,25,26] In a large multi-hospital study, Saver et al. demonstrated that earlier IV alteplase initiation after symptom-onset (in 15-min increments) resulted in reduced inpatient mortality, reduced symptomatic intracranial hemorrhage, improved independent ambulation at discharge, and improved likelihood of discharge to home.[13] A recent study showed longer-term benefits in the form of reduced 1-year all-cause mortality and all-cause readmissions, with every 15-min reduction in IV alteplase initiation time after hospital arrival.[17] Saver also estimated that for every hour an AIS goes untreated, the damage done to the neurons in the brain is the equivalent of aging 3.6 years.[27] Unlike our study that did not demonstrate stroke hospitalization-related cost savings for lower door-to-needle times, past studies have demonstrated cost savings for alteplase versus placebo administration. Fagan et al. also assessed the use of alteplase (as compared with placebo) and found that the treatment reduced hospital LOS and resulted in higher discharges to homes instead of inpatient rehabilitation or nursing homes, thereby resulting in cost savings.[26] Given that this study and others before have established various benefits of early alteplase treatment, it is essential to examine factors that are important determinants of delays in alteplase administration in various health systems. These factors could include lack of "last known well" or "symptom onset" information, lack of information about recent anticoagulant use, lack of recognition of stroke symptoms, and the existence of other ailments and comorbidities that prevent quicker physician decision-making for alteplase initiation. Future studies are required to identify factors that are important determinants of delays in alteplase administration, so that interventions to address these factors can be developed.

It is important to note that this study found statistically significant benefits of early IV alteplase treatment with respect to mRS at discharge, but did not find similar benefits for disability at discharge. mRS and disability at discharge are positively correlated in this study. More than 95% of patients with disability at discharge had an mRS of more than 2. Moreover, more than 40% of patients who were discharged home had an mRS of more than 2. This suggests that some patients who were sicker were discharged home. One primary reason, based on the patient population served in this study, could be lower insurance level and lack of financial ability for some pateints, which makes it harder for these patients to be discharged to other inpatient facilities. They are discharged home even though they need more care due to limited financial ability to seek more inpateint care. If the regressions adjusted for level of insurance (and not just type), and patient's financial status (income/wealth), the study might have been able to control for these unobserved socio-economic differences. Consequently, in this study, the mRS is a more sensitive measure of how sick a patient is at discharge, than the disability at discharge, since disability at discharge is contingent on discharge to other inpatient care facilities and is potentially confounded by unobserved socio-economic status.

This study has certain limitations. First, the study utilizes data from one health system in Greater Houston and hence national generalizations of the study findings might be restricted. Second, the data do not have all patient-level socio-economic variables such as income, which might have explained some of the unobserved differences in discharge dispositions and other outcomes. Third, the study did not have cost and general healthcare utilization information after the patient's discharge from MHHS, only had 30-day readmission information if the patient was re-admitted to MHHS, and had clinical outcomes only up to 90-days after the stroke incidence. Nevertheless, MHHS is the largest health system in Greater Houston, and given Houston's highly socio-demographically and clinically diverse population, these findings have considerable clinical implications for the nation. Also, given the availability of EMR and financial data, and the study team's meticulous data quality checks, the study data are particularly rich and high quality.

This study provides evidence supporting AHA's new recommendation of 30 min or less door-to-needle time based on clinical outcomes at discharge and 90 days, as well as efficiency of care outcomes, specifically lower LOS. Improved clinical outcomes, such as mRS and NIHSS are often associated with better cognitive performance and quality of life at discharge, and during the first year after discharge. They are probably also associated with reduced healthcare utilizations during the first and subsequent years after discharge, as a result of discharging patients with better clinical and performance status. Hence, future studies are required to examine cognitive, quality of life, long-term mortality, and long-term cost outcomes

associated with administration of alteplase within 30 min of hospital arrival. Future studies are also required to identify factors that are important determinants of delays in alteplase administration in various health systems, so that interventions to address these factors can be developed.

Acknowledgment

This manuscript was sponsored by F. Hoffmann-La Roche Ltd./Genentech, Inc.

Author Contributions

SSR designed the study, contributed important analytic tools, oversaw and performed data collection and cleaning, analyzed data, interpreted the data/analysis, drafted the manuscript, provided critical revisions for important intellectual content, approved the final version, and agrees to be accountable for all aspects of the work. MDP contributed to the study design, interpreted the data/analysis, provided critical revisions for important intellectual content, approved the final version, and agrees to be accountable for all aspects of the work. JW assisted in data collection and cleaning, approved the final version, and agrees to be accountable for all aspects of the work. TD extracted and cleaned the healthcare system as well as financial data, provided critical revisions for important intellectual content, approved the final version, and agrees to be accountable for all aspects of the work. CS contributed to the study design, provided critical revisions for important intellectual content, approved the final version, and agrees to be accountable for all aspects of the work. SIS designed the study, facilitated data access and collection, interpreted the data/analysis, provided critical revisions for important intellectual content, approved the final version, and agrees to be accountable for all aspects of the work. SSR had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Conflict of Interest

All authors received support from F. Hoffmann-La Roche Ltd/Genentech, Inc. during the conduct of this study, including editorial support. MDP and CS are employees of Genentech, Inc.

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