Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ __10/31/117_____
Anika Backster Date

Time to tPA and Associations with 30 day Readmission and Mortality and 1 year Mortality.

By Anika Backster M.D.
Master of Science in Clinical Research

_____

David W. Wright M.D.
Advisor

_____

Audrey Flak Pennington, PhD, MPH
Committee Member

_____

Amita Manatunga PhD
Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____

Date

Time to tPA and Associations with 30 day Readmission and Mortality and 1 year Mortality.

By Anika Backster
B.S., University of California, Riverside, 2002
M.D., University of Illinois, Chicago, 2008

Advisor: David W. Wright, M.D.

An abstract of
a thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of Master of Clinical Research

2017

Abstract

Time to tPA and Associations with 30 day Readmission and Mortality and 1 year Mortality.

By Anika Backster

Background

The southeastern US has the dubious distinction of having the highest US concentration of stroke patients with the highest morbidity and mortality in the U.S. Identifying factors that mitigate the devastating effects of acute stroke and reduce readmissions would have a large impact on patients, families, and society. Shortening time to Tissue Plasminogen Activator (tPA) administration is one factor that may improve patient outcomes.

Objectives

Among acute ischemic stroke patients, examine the association between Emergency Department (ED) door to tPA (dtPA) infusion time and 30-day readmissions and mortality, as well as 1-yr mortality, using a cohort created by data linkage among the Georgia Coverdell Acute Stroke Registry (GCASR) and other Georgia databases.

Methods

A retrospective cohort of acute stroke patients receiving tPA in the ED was identified from the GCASR database (2008-2013) and linked to Georgia hospital discharge and death records using Fine-grained Record Integration and Linkage software (FRIL). Risk factors for 30-day mortality and admissions were analyzed using multivariable logistic regression.

Results

2691 patients were available for primary outcome analysis and linkage. DtPA time was not significantly associated with 30-day readmission in crude or adjusted analysis. DtPA time was associated with 30-day mortality in crude analysis: 61-90 minute OR 1.59 (95% confidence interval 1.20-2.10) and 91+ minute OR 1.43 (95% confidence interval 1.05-1.94). DtPA time was also associated with 1 year mortality in crude analysis: 61-90 minute OR 1.59 (95% confidence interval 1.27-1.98) and 91+ minute OR 1.43 (95% confidence interval 1.05-1.94).

Conclusion

Door-to-tPA time was associated with decreased 30-day and 1-year mortality though we found no evidence of an association with decreased 30-day readmission.. Our results strengthen the concept that door to tPA time is an important clinical target for process initiatives as it may decrease overall stoke mortality.

Time to tPA and Associations with 30 day Readmission and Mortality and 1 year Mortality.

By Anika Backster, M.D.
B.S., University of California, Riverside, 2002
M.D., University of Illinois, Chicago, 2008

Advisor: David W. Wright, M.D.

A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of Master of Clinical Research

2017

AKNOWLEDGMENTS

I would like to acknowledge the Georgia Dept Public Health and Dr. Moges Ido for his work on the statics, and Dr. Rana Bayakly for support and access to the databases. Also Dr. Michael Frankel (Dept of Neurology Chair, Grady Memorial Hospital, and Coverdell Registry cofounder), and Dr. Beau Bruce for their help with the early design of the project. Supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR002378. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

TABLE OF CONTENTS

LIST OF FIGURE AND TABLES

TABLES

Introduction

Stroke is the third leading cause of death and disability in the United States. An estimated 3.3 million people in the U.S. visit hospitals annually with a primary diagnosis of stroke(1). Compared to the rest of the U.S. population, the southeastern United States has the unenviable designation of being labeled the "stroke belt" due to a disproportionately high number of stroke diagnoses compared to the rest of the U.S. Furthermore, the state of Georgia is unique in that approximately 25% of strokes occur in people under 55 years of age with African Americans making up approximately 30% of the stroke population(2). Solidifying modifiable clinical factors that impact the outcome of acute stroke, such as door to tissue plasminogen activator (tPA) time, is needed to help form important process improvement initiatives in order to improve patient outcome.

The Centers for Medicare and Medicaid Services (CMS) is a leader in process improvement with the goal of improved disease outcomes and decreased expenditures. Currently under the CMS Readmissions Reduction Program (CMS-1607F), 5 common medical ailments have 30-day readmissions tied to financial reimbursement penalties. This increased hospital accountability has heightened interest in examining ways to mitigate 30-day readmissions. Already the CMS has created hospital outcome measures for stroke(3). With stroke included as part of the Hospital Inpatient Quality Reporting (IQR) Program, it was originally postulated that as early as 2017, acute stroke patients would be included in the CMS Readmissions Reduction Program, but has not to date. As stroke admissions and readmissions continue to be monitored by CMS, adding it to the Readmissions Reduction Program remains likely in near future. It is

prudent both medically and financially to improve overall stroke management by better understanding how door to tPA time can be used to influence and decrease stroke readmissions.

tPA is a therapy shown to be associated with odds of a favorable outcome in the form of neurologic improvement three months after stroke(4). Early treatment, within 3 hours of stroke onset, is a critical factor for patient tPA treatment eligibility and improved outcome. It has been postulated that "time is brain" and that the earlier the treatment, the better outcome. However, there is no population-based data linking timely reperfusion in stroke to improved outcomes(5). Furthermore, no large studies have been published on the shorter, 30-day outcome timeframe for readmission or death. As emergency physicians who initiate a patient's hospital experience, we are best poised to influence door to tPA treatment time. We have used a population-based health database to further examine the effects of emergency department time until tPA on two important patient 30-day outcomes—readmission and mortality—and an important clinically significant outcome of 1-year mortality.

BACKGROUND

Stroke treatment is estimated to cost $34 billion annually in the US(6). Due to its prominence as a national healthcare concern, it is often a target area for nationwide incentives. The Healthy People 2020 campaign is a program created by the U.S. Department of Health and Human Services to increase the quality and years of healthy life in the population. With regards to stroke, the Healthy People 2020 objectives include "to reduce stroke deaths (HDS-3)" and

"increase the proportion of eligible patient with strokes who receive acute reperfusion therapy within 3 hours from symptom onset from 74.1% to 81.5%(HDS-19.3)"(7). The CMS Readmissions Reduction Program together with the Healthy People 2020 program are large scale governmental examples of the emphasis our government is placing on improving stroke outcomes.

tPA is a medication widely accepted to improve stroke outcomes but only under strict circumstances. Per tPA administration guidelines, all patients with diagnosis of acute ischemic stroke causing measureable deficit, onset of symptoms occurring less than 3 hours prior to administration, and older than 18 years of age should be strongly considered for tPA administration. tPA is shown to be associated with odds of a favorable outcome in the form of neurologic improvement three months after stroke(4) and seems to provide the most benefit when administered within 90 minutes of symptom onset(8, 9). While evidence points to a continuous relationship between shorter door to tPA (dtPA) and better outcomes, this remains unproven. Pooled analysis has shown that use of tPA decreases mortality and dependent activities of daily life(10). In recognition of these benefits the rate of thrombolysis (use of tPA) has increased from 43%-77% amongst eligible patients from 2004-2011(11).

Even so, controversy is seen amongst the scientific community (especially amongst emergency physicians) regarding its risk benefit profile over concerns for increased rates of bleeding(12, 13). In 2015 under the pressure of controversy and with an absence of Class I evidence, the American College of Emergency Physicians (ACEP) Clinical Policies Committee proposed guidelines to

downgrade the use of tPA administered within 3 hours to a Class B recommendation(14).

Emergency physicians are integral to establishing if a patient meets criteria for tissue plasminogen activator (tPA) and to initiating intravenous tPA within a goal of 60 minutes from hospital arrival. Sometimes they are able to collaborate with neurologists but in more rural areas this may not be possible and the decision making process may fall entirely on them. When timeliness to intervention is key, engagement of emergency physicians is likewise tantamount. In accordance with the American Heart Association (AHA) and American Stroke Association (ASA) Physicians Guidelines, emergency physicians are responsible for initial stroke management. Emergency physicians are to evaluate the time frame of occurrence, ensure the patient receives a CT scan of the head within 25 minutes, establish if the patient meets criteria for tissue plasminogen activator (tPA) and initiate intravenous tPA within 60 minutes of arrival(15). In rural areas such decisions may be done with minimal to no input from a neurologist. Emergency physicians are a key link in the timeline of providing rapid intervention and further studies demonstrating the efficacy of tPA are needed to get everyone on board.

This study aims to better examine the relationship between dtPA time and stroke outcomes in one of the areas of the US most inundated with strokes using large statewide databases.

Databases

Three databases were used for this study, the GCASR to identify subjects with acute stroke treated with tPA, the Georgia Hospital discharge database for readmission information, and Georgia state death records for mortality.

The Georgia Coverdell Acute Stroke Registry (GCASR) is a unique population-based database developed in the state of Georgia as a means to address quality improvement in all areas of stroke care. The database is funded by the Centers for Disease Control and Prevention (CDC) and has been incorporated into the Georgia State Division of Public Health since 2005. It is run as a partnership between the CDC, Emory University, the AHA/ASA, the Georgia Hospital Association (GHA), and affiliated hospitals(16). Using this robust database and statistical linkage techniques between state hospital discharge and mortality records, we have been able to more closely examine the relationship between timeliness in receiving tPA and readmission and mortality rates.

GCASR is a unique data source established to provide a monitoring system for measures of clinical performance and to support improving the quality of care provided to acute stroke patients nationally, however only data for those admitted in Georgia hospitals were used for this study. Named after the late Georgia senator Paul Coverdell who died from an acute stroke, it was started in 2001 with collaboration of the CDC. It is housed at the Georgia Department of Public Health and serves as the source to identify acute ischemic stroke patients treated with intravenous tissue plasminogen activator (tPA). Dr. Michael Frankel (Lead Neurologist for Georgia Coverdell Acute Stroke Registry, Chief of Neurology and director of the Marcus stroke and neuroscience center at Grady

Memorial Hospital) a co-mentor, was the initial PI and current chief neurologist of the registry, and Dr. David Wright (PI of the southeastern hub for NETT network and the Director of the Emory Emergency Neurosciences division in the Department of Emergency Medicine at Emory University) my primary mentor, assisted with developing the original registry as well. Further assistance and access to the registry came by way of Ms. Rana Bayakly (PI GCASR) and Dr. Moges Ido (MD MPH Epidemiologist GCASR).

Membership to GCASR is voluntary. As of 2013, 66 hospitals across the state of Georgia participated, capturing an estimated 79% of the acute strokes occurring in the state(16). Distribution of participating hospitals is scattered with an apparent higher percentage of participating hospitals occurring in more urban areas compared to the rural. Determination of data elements collected occurred via an expert panel convened by the CDC in 2001, who reached consensus on what elements would best improve the quality of stroke treatment. Since establishment, the database undergoes revisions to elements about every two to three years. Data for GCASR is populated by collection of onsite trained stroke coordinators who input data mostly in real time, and sometimes from chart abstraction.

The Georgia discharge database system comes from data collected on all patients hospitalized in non-federal acute care or critical care facilities in the state of Georgia. It is collected and maintained by the Georgia Hospital Association (GHA) with the goal of better measuring the quality of healthcare through objective data-based methods. Data is housed with the GHA and is available to the Georgia Department of Public Health for surveillance purposes.

Information collected includes the socio-demographic characteristics of the patient, disease diagnosis of the patient, interventions received, and event dates. Records were available for our use up through December 31, 2010. These data were used to identify readmission to any acute care facility within the state of Georgia.

Georgia state death records data was the source of patient vital status (mortality) and was collected by the Vital Records office of the Georgia Department of Public Health.

FRIL

In order to link de-identified data, Fine-grained Record Integration and Linkage (FRIL) software was used. FRIL is a relatively nascent SAS (version 9.3, SAS Institute, Inc) software application for matching data records. It performs multistage probabilistic matching between records so that subjects do not have to be re-identified from a database in order to follow them up in another database. A recent study showed that data linkage using this method is accurate to the 90th percentile for multiple variables, and that failure to link does not increase bias though it may lower estimates of mortality(17).

Summary

This study takes a somewhat unique U.S. population of acute stroke patients and analyzes the ED modifiable effect of door to tPA (dtPA) on two patient centered metrics, death and readmission. We looked at these metrics at two end points—30 days in response to CMS monitoring and 1 year which is likely more clinically relevant—and created a study that provides important

insight and affirmation to process modifications needed to improve overall patient outcomes and reduce readmission and mortality.

METHODS

Hypothesis

In acute ischemic stroke patients, a shorter door to tPA infusion time will be associated with decreased 30-day readmission rates and mortality and 1-year mortality.

Study Design:

A retrospective cohort study of acute stroke patients in the state of Georgia.

Data sources:

Three data sources—the 2008-2013 Georgia Coverdell Acute Stroke Registry (GCASR), the 2008-2013 Georgia hospital discharge data, and the 2008-2014 Georgia death records—were used to assess the impact of door-to-needle time on readmission and mortality in acute stroke patients treated with IV tPA. The data sources were linked using both probabilistic and hierarchical deterministic methods

Data Linkage:

The linkage consisted of two parts [Figure 1]: first the GCASR data were linked to the Georgia hospital discharge data using a hierarchical deterministic method, and then the output was linked with death data applying a previously tested multistage probabilistic linkage procedure (sensitivity 92% and specificity 100%)(17). The GCASR data contains only non-identifying information including

age, sex, race, date of admission and discharge, and facility code. The linkage with the hospital discharge data was based on the assumption that no two subjects with similar demographic characteristics would be admitted on the same date at the same facility with acute stroke. The procedure resulted in a reasonably acceptable yield (87%) with an excellent rate of true matches (positive predictive value 96%)(18) on test data. All linkages were performed using Fine-grained Records Integration and Linkage (FRIL) tool version 2.1.5(19, 20).

Study Population:

Per guidelines for indications for IV tPA administration, the following subjects with stroke have contraindications for the use of IV tPA(15) and thus have been implicitly excluded: head trauma or stroke within the past 3 months, symptoms suggesting subarachnoid hemorrhage (or CT demonstrating such), CT demonstrating multilobar infarction, history of intracranial hemorrhage, intracranial neoplasm or arteriovenous malformation, intracranial or spinal surgery in past 3 months, active internal bleeding, active bleeding diathesis, blood glucose <50mg/dl. Relative contraindications for the use of tPA include: minor/rapidly improving stroke symptoms, pregnancy, seizure, major surgery/severe trauma within 14 days, hemorrhage within 21 days, and acute myocardial infarction within 3 months.

A total of 3,600 records of acute stroke patients treated with IV tPA were captured by the registry over the 6-year period of January 1, 2008 – December 31, 2013.[Fig-1] Among these, 367 were excluded because they refer either to in-hospital stroke or to non-ischemic stroke or patients received IV tPA but were not admitted. Of the remaining 3,233 records, 2,898 (89.6%) were linked with the

hospital discharge data but only 2,777 had LONGID, the data element necessary for linking with the death data and determining readmission. Patients who received IV tPA twice or as part of a clinical trial and patients who were under 18 years of age were excluded from the analyses.

Outcome Measures & Predictors:

The main outcomes of interest were death at 30-days and 1-year and readmission within 30-days of hospital discharge regardless of the underlying cause. Death was examined at 30 days or 365 days after admission. Readmission was examined at 30 days after hospital discharge in keeping with CMS Readmissions Reduction Program definitions. Subjects were considered to be alive if neither the hospital discharge data reported them as having "Expired" under final discharge disposition nor they were captured in the Georgia state death record. Readmission to a different facility within a day from the index admission date was considered as a transfer rather than a readmission.

Door-to-needle time, the primary predictor, was defined as the time difference between patient arrival at a hospital to the initiation of IV tPA. The following variables were considered plausible confounders of the time-outcome association based on clinical knowledge: patients' socio-demographic characteristics (age, sex, race, and insurance status), hospital characteristics (hospital size/number of beds, primary stroke center status, duration of hospital enrolment in GCASR, and urbanity), event characteristics (time last known well until hospital arrival, time of day, and NIH Stroke Scale score), and patient medical history (hypertension, dyslipidemia, coronary artery disease/prior

myocardial infarction, diabetes mellitus, smoking, atrial fibrillation/flutter, previous stroke, heart failure, peripheral vascular disease, carotid stenosis, TIA).

Statistical Analysis:

Accuracy of database linkage was assessed descriptively comparing distribution of patient and hospital characteristics among records "listed for linkage" and those "linked". [Appendix table 1]. A difference of 1%-2% was considered negligible indicating that the merge between the datasets was successful (i.e. that the probability of a successful merge between the two datasets did not depend on the characteristic examined and is accurate).

The outcome door to needle time was categorized into 0-60 minutes, 61-90 minutes, and >90 minutes categories based on commonly held clinical intervals of significance. Descriptive statistics were used to compare patient characteristics by door to needle time. The measure of stroke severity, NIH stroke scale score, had 9.9% missing values. Hence, 20 replicates of the data were imputed assuming a general missing pattern and values were missing at random. The association between door to needle time and the outcomes of 30-day and 1-yr mortality as well as 30-day readmission were assessed using generalized estimating equations (GLIMMIX procedure) controlling for confounders and in-hospital correlation and considering hospital as a random variable. The multivariable analyses were done both on complete and imputed datasets. Patients from hospitals with less than five cases were excluded because of lack of stable estimates. Almost all patients were treated in primary stroke center (97.9%) located in metropolitan area (98.4%), these two variables were dropped from the multivariable analyses because they lacked discriminatory power. All

Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

IRB:

Both the Emory and Georgia Department of Public Health IRBs approved this project after review.

RESULTS

Characteristics of Study subjects:

2,691 acute stroke patients received tPA in the emergency department, of these 338 (12.6%) suffered mortality within 30-days admission and 586 (21.8%) suffered mortality within 1-year of admission. 238 (8.8%) were readmitted within 30-day discharge [Figure 1].

Patient characteristics are shown in Tables 1 A-C. Gender was evenly distributed (48.8% males to 51.2% females) and the majority of patients were white (60.2%) [Table 1A]. The majority (80.5%) of patients had hypertension [Table 1B]. Most patients were treated at large metropolitan/urban hospitals (97.7%) and primary stroke centers (98.4%). 4.8% had symptomatic intracranial hemorrhage [Table 1C].

Tables 2 A-B displays dtPA by patient characteristics and outcomes using Chi squared and Wilcoxon tests. Statistical significance ($P<0.05$) was noted with gender, race, NIH stroke score, Diabetes, Atrial fibrillation, last known well (LKW), time part of GCASR, metropolitan location, primary stoke center designation, time of day, and hospital size. Mortality at both 30-days and 1-year was also significant.

Tables 3 A-F examine relative risk between 30-day readmission and mortality as well as 1-year mortality by complete and imputed data. Characteristics with significant association for 30-day readmission were NIHSS 8-12 (complete data), time of day (imputed data), and prior stroke (both complete and imputed data). Characteristics with significant association for 30-day mortality were dtPA >91 minutes (imputed data), dtPA 61-90 minutes (complete and imputed data), older age 75 and up (complete and imputed data), NIHSS (complete and imputed data), and A.fib/flutter (complete and imputed data). Characteristics with significant association for 1-year mortality were dtPA >91 minutes (imputed data), dtPA 61-90 minutes (complete and imputed data), older age (complete and imputed data), NIHSS (complete and imputed data), A.fib/flutter (complete and imputed data), and heart failure (complete and imputed data).

Main results:

The median door to needle time was 69 minutes for acute ischemic stroke patients having received tPA (IQR 52-92 minutes).

In multivariable logistic regression models door to needle time was not associated with 30 day readmission in adjusted analysis, crude analysis did not show association either [Table 4]. Crude analysis of mortality yielded the same increased odds of death for both 30-day and 1-year in both exposure groups. Crude analysis of 30-day mortality was significantly associated showing an increased odds of death for both the 61-90 minute OR 1.59 (95% confidence interval 1.20-2.10) and 91 and up OR 1.43 (95% confidence interval 1.05-1.94) groups. 1-year mortality was significantly associated showing an increased odds

of death for both the 61-90 minute OR 1.59 (95% confidence interval 1.27-1.98) and 91 and up OR 1.43 (95% confidence interval 1.05-1.94) groups. Adjusted 1-year mortality showed only significant association in the 61-90 minute group, OR 1.45 (95% confidence interval 1.08-1.94).

DISCUSSION

In this study of acute ischemic stroke patients receiving tPA we did not find an association between dtPA and 30-day readmissions. 30 days was chosen as a time period of interest because it is a time marker for CMS reimbursement of hospitals with other diseases. That dtPA does not appear associated with this outcome should allow hospitals to breath a sigh of relief.

However we did find an association between dtPA and 30-day mortality as well as 1-year mortality in crude analyses, with those receiving tPA between 61-90 minutes 1.6 times more likely to have 30-day and 1-year mortality than those who received tPA under 60 minutes. Compared to a metaanalysis with a mortality rate of 13.5% within 30 days (mortality rate 17.9% at 90days) (21), our mortality rate of 12.6% at 30 days in this study was similar. To our knowledge this is the first time 30 day readmission rate is being examined thus no comparison exists. This is the first study to look at the ED modifiable factor of door time to tPA and the clinically and financially relevant outcomes of death and readmission in the 30 days after and death one year after stroke.

Our findings add to the existing body of literature evaluating the medication influence of tPA delivery time on stroke outcomes, with the important distinguisher that it evaluates door to tPA time, an exposure that clinicians can

readily modify. Prior studies have evaluated outcomes in the context of use of tPA in the timeframe of symptom onset to administration(21, 22). But affecting what occurs outside of the hospital (e.g. social recognition of symptoms and distance from hospital) is more challenging, and sometimes not feasible, as opposed to making changes to a process within the hospital like stroke notification and tPA delivery. Like other studies, our study suggests that tPA delivered under 60 minutes yields better outcomes compared to after 60 minutes for both 30 and 365-day mortality (table 4).

Symptomatic intracranial hemorrhage in this study was noted for a slightly lower rate of 4.8% compared to the 6.8% found in a meta-analysis by Emberson and colleagues(21). It is doubtful that NIHSS is related as our cohort showed moderate stroke severity score (median of 11). Possible reasons for the decrease seen in our study include the somewhat unique patient population of Georgia with it being in the U.S. "stroke belt" and having more frequent strokes our major stroke centers are well rehearsed and used to giving tPA frequently and may have less side effects as a result.

This study is also of note for its successful use of the novel linkage technique, FRIL, that allows analysis of de-identified data in a way that preserves anonymity yet can allow follow-up analysis of patients (depending on what databases are chosen for linkage). Overall, we believe that our linkage of patients is reliable and likely very accurate. Continued validation of the FRIL tool could potentially significantly expand use of database analyses.

Limitations:

Failure to link is known to increase with database size. While it is possible that this may have affected our results, it is unlikely as FRIL linkage was checked for accuracy using the aforementioned comparison between those listed for linkage and those successfully linked.

While this study was designed to look the emergency department modifiable factor of dtPA time, many factors influence out-of-hospital time and it is possible that they may affect the outcome as well. For example, the patient may decide to wait 3 hours before coming in for evaluation, moving overall time from symptom onset to tPA administration closer to the 240 minute mark. If timeliness is the most important factor and a precise factor, then having a large number of patients delaying time to ED presentation may affect results. However, this study was intentionally not designed to analyze all potential out of hospital modifiers as they are clinically difficult to modify.

As a retrospective study based on database entry it is potentially subject to entry errors and time misinterpretations. Coverdell database entries are performed by a designated person at each site, and the person obtains the information from chart extraction (not in real time). Also as only state based databases were used, persons could have been lost to follow up who were readmitted or died out of state.

Finally, dtPA reflects only one point in acute stroke management. We were not able to account for in-hospital or out of hospital course. Some of these time components such as discharge dispositions are likely important and potentially modifiable factors in affecting acute stroke outcomes.

Conclusion

Door to tPA time is a clinically modifiable factor where a shorter time has been shown to improve outcomes. In this study it was associated with decreased 30-day and 1-year mortality though we found no evidence of an association with decreased 30-day readmission. Door to tPA is a readily modifiable factor around which individual hospitals can create process improvement initiatives aimed largely at their emergency and neurology departments to speed up the flow of getting brain imaging and determining NIH stroke scales and thus improve time to administering tPA. Continued larger and prospective studies of dtPA and the outcomes of decreased 30 day readmissions and 30 day mortality are needed to examine these relationships. Our results strengthen the concept that door to tPA time is an important clinical target for process initiatives as it may decrease overall stoke mortality.

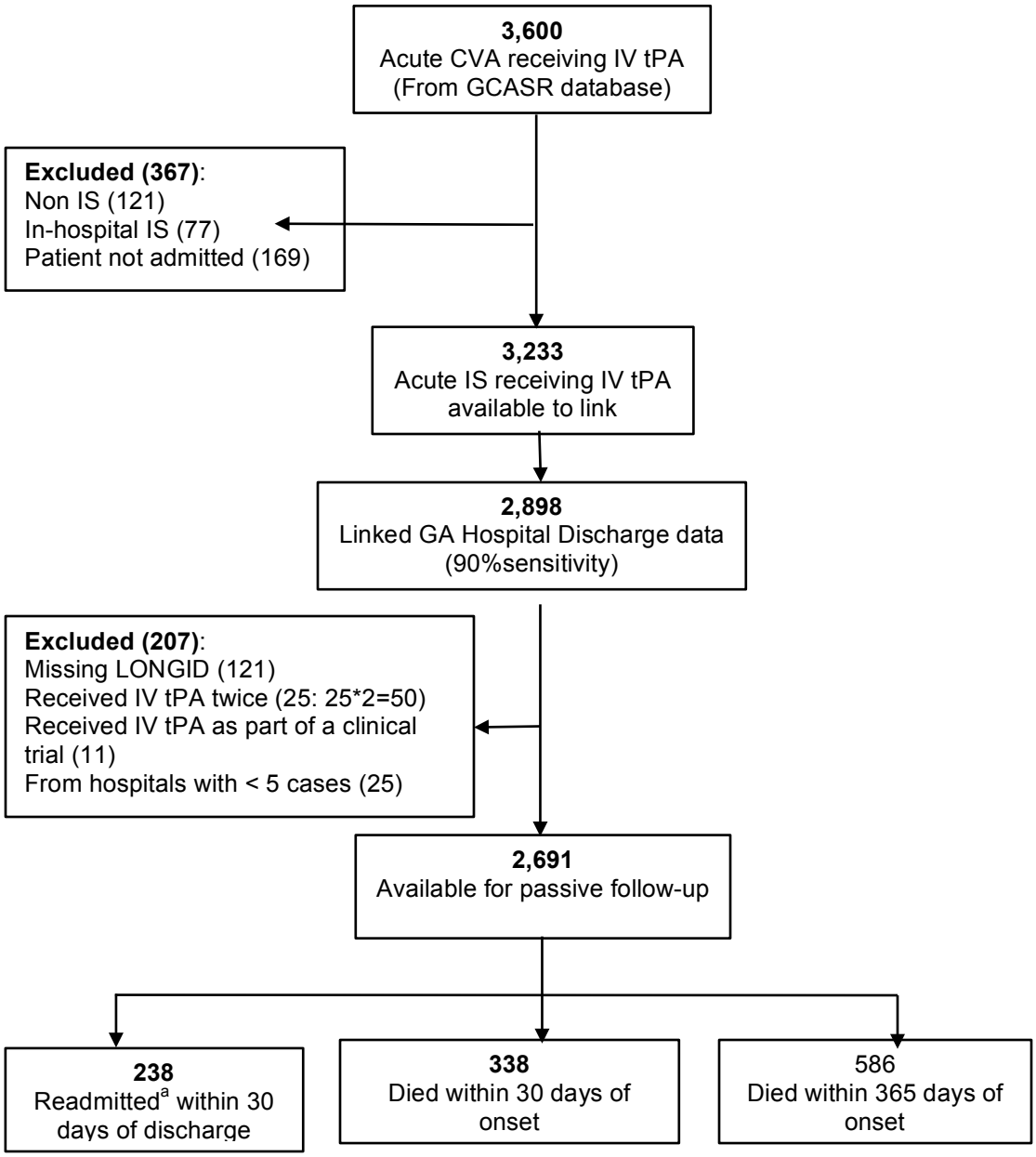
REFERENCES

1. Pitts SR, Niska RW, Xu J, et al. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. *National health statistics reports* 2008(7):1-38.
2. Reeves MJ, Arora S, Broderick JP, et al. Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. *Stroke; a journal of cerebral circulation* 2005;36(6):1232-40.
3. Fonarow GC, Alberts MJ, Broderick JP, et al. Stroke outcomes measures must be appropriately risk adjusted to ensure quality care of patients: a presidential advisory from the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation* 2014;45(5):1589-601.
4. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *The New England journal of medicine* 1995;333(24):1581-7.
5. Newman DH, Schuur JD. Streetlights and quality measures for stroke. *Annals of emergency medicine* 2014;64(3):245-7.

6. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation* 2015;131(4):e29-322.
7. Healthy People 2020 objectives: Heart Disease and Stroke. 2016. (https://http://www.healthypeople.gov/2020/topics-objectives/topic/heart-disease-and-stroke/objectives?topicId=21). (Accessed 8-29-16 2016).
8. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology* 2000;55(11):1649-55.
9. Saver JL, Smith EE, Fonarow GC, et al. The "golden hour" and acute brain ischemia: presenting features and lytic therapy in >30,000 patients arriving within 60 minutes of stroke onset. *Stroke; a journal of cerebral circulation* 2010;41(7):1431-9.
10. Wardlaw JM. Murray V. Berge E. dZG. Thrombolysis for Acute Ischemic Stroke. *Cochrane Database* 2009.
11. Schwamm LH, Ali SF, Reeves MJ, et al. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at Get With The Guidelines-Stroke hospitals. *Circulation Cardiovascular quality and outcomes* 2013;6(5):543-9.
12. Brown SG, Macdonald SP, Hankey GJ. Do risks outweigh benefits in thrombolysis for stroke? *BMJ (Clinical research ed)* 2013;347:f5215.
13. Scott PA, Xu Z, Meurer WJ, et al. Attitudes and beliefs of Michigan emergency physicians toward tissue plasminogen activator use in stroke: baseline survey results from the INcreasing Stroke Treatment through INteractive behavioral Change Tactic (INSTINCT) trial hospitals. *Stroke; a journal of cerebral circulation* 2010;41(9):2026-32.
14. Brown MD, Burton JH, Nazarian DJ, et al. Clinical Policy: Use of Intravenous Tissue Plasminogen Activator for the Management of Acute Ischemic Stroke in the Emergency Department. *Annals of emergency medicine* 2015;66(3):322-33 e31.
15. Jauch EC, Saver JL, Adams HP, Jr., et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation* 2013;44(3):870-947.
16. DPH Georgia Department of Public Health. 2016. (http://dph.georgia.gov/georgia-coverdell-acute-stroke-registry). (Accessed 8-29-16 2016).
17. Ido MS, Bayakly R, Frankel M, et al. Administrative data linkage to evaluate a quality improvement program in acute stroke care, Georgia, 2006-2009. *Preventing chronic disease* 2015;12:E05.
18. Ido MS, Frankel MR, Okosun IS, et al. Quality of Care and Its Impact on One-Year Mortality: The Georgia Coverdell Acute Stroke Registry. *American journal of medical quality : the official journal of the American College of Medical Quality* 2017:1062860617696578.

19. Jurczyk P, Lu JJ, Xiong L, et al. FRIL: A tool for comparative record linkage. *AMIA Annual Symposium proceedings / AMIA Symposium AMIA Symposium* 2008:440-4.
20. Jurczyk P, Lu JJ, Xiong L, et al. Fine-grained record integration and linkage tool. *Birth defects research Part A, Clinical and molecular teratology* 2008;82(11):822-9.
21. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet (London, England)* 2014;384(9958):1929-35.
22. Campbell BC, Meretoja A, Donnan GA, et al. Twenty-Year History of the Evolution of Stroke Thrombolysis With Intravenous Alteplase to Reduce Long-Term Disability. *Stroke; a journal of cerebral circulation* 2015;46(8):2341-6.

Figure 1 Data Linkage, GCASR data 2008-2013



a: among acute ischemic stroke patients discharged home and did not die in the first 30 days post discharge

Tables

Table 1A: Distribution of Intravenous tPA[a] treated ischemic stroke patients by socio-demographic characteristics, and disease severity, Georgia Coverdell Acute Stroke Registry, 2008-2013 (N=2,691)

Patient Characteristic	N (%)
Gender	
Male	1,313 (48.8)
Female	1,378 (51.2)
Race	
White	1,618 (60.2)
Black	990 (36.8)
Other	81 (3.0)
Age[b]	
< 50Years	422 (15.7)
50-65 Years	817 (30.4)
66-75 Years	561 (20.9)
76+ Years	891 (33.1)
Primary Insurance Source	
Medicare	987 (36.8)
Medicaid	124 (4.6)
Personal insurance only	687 (25.6)
Two or more sources	513 (19.1)
Self-pay/No Insurance	369 (13.8)
NIH Stroke Scale Score Median (IQR)	
	11 (6, 18)

[a] tPA= tissue plasminogen activator
[b] median age of 67 (IQR 56,79)

Table 1B: Distribution of Intravenous tPA[a] treated ischemic stroke patients by past medical history, Georgia Coverdell Acute Stroke Registry, 2008-2013 (N=2,691)

Previous Medical History	N (%)
Hypertension	2,000 (80.5)
Dyslipidemia	955 (38.4)
Coronary artery disease/prior Myocardial Infarction	615 (24.8)
Diabetes mellitus	687 (27.7)
Smoking	564 (22.7)
Atrial fibrillation/flutter	478 (19.2)
Previous stroke	489 (19.7)
Heart failure	268 (10.8)
Peripheral vascular disease	80 (3.2)
Carotid stenosis	47 (1.9)
Prosthetic heart valve	28 (1.1)
Current pregnancy	0 (0)
Sickle Cell	1 (0.04)
No history of medical illness	206 (7.7)

[a] tPA= tissue plasminogen activator

Table 1C: Distribution of Intravenous tPA[a] treated ischemic stroke patients by hospital and event-related characteristics, Georgia Coverdell Acute Stroke Registry, 2008-2013 (N=2,691)

Hospital & Event Related Characteristic	N(%) else Median(IQR)
Last Known Well to Hospital Arrival Time (minutes) IQR	60 (40, 90)
Door-to-Needle Time (minutes)	69 (52, 92)
Hospital Length of Stay (days)	5 (3, 8)
Time Since Enrollment in GCASR to Treatment of Patient (days)	1,818 (1,198, 2.385)
Discharge Disposition	
Home	1,240 (46.1)
Hospice - Home	41 (1.5)
Hospice - Health care facility	129 (4.8)
Acute care facility	63 (2.3)
Other health care facility	1,021 (37.9)
Expired	185 (6.9)
Left against medical advice	12 (0.5)
Hospital Location	
Non-metropolitan	56 (2.1)
Metropolitan	2,635 (97.9)
Primary Stroke Center Status	
No	43 (1.6)
Yes	2,648 (98.4)
Time of day[b]	
Day	1,723 (64.3)
Night	956 (35.7)
Hospital Size	
< 101 beds	26 (1.0)
101-250 beds	348 (12.9)
251-400 beds	664 (24.7)
401+ beds	1,653 (61.4)
Symptomatic Intracranial Hemorrhage	
	120 (4.8)

[a] tPA= tissue plasminogen activator

[b] Day time is defined as 6AM-6PM

Results Tables

Table 2A: Door to tPA[a] time by patient characteristics, GCASR 2008-2013

Variable	≤60 min dtPA N(%)	61-90 min dtPA N(%)	≥91 min dtPA N(%)	p-value[b]
Gender				<.0001
Male	554 (54.8)	438 (46.7)	303 (43.1)	
Female	457 (45.2)	500 (53.3)	400 (56.9)	
Race				0.032
White	582 (57.62)	575 (61.3)	439 (62.54)	
Blacks	399 (39.5)	326 (34.75)	249 (35.47)	
Other (Asian)	29 (2.87)	37 (3.94)	14 (1.99)	
Age (IQR)				0.105
≤ 50 Years	159 (15.73)	129 (13.75)	127 (18.07)	
51-65 Years	322 (31.85)	275 (29.32)	207 (29.45)	
66-75 Years	212 (20.97)	193 (20.58)	148 (21.05)	
76+ Years	318 (31.45)	341 (36.35)	221 (31.44)	
Primary Insurance Source				0.711
No health insurance/self-pay	138 (13.6)	133 (14.2)	94 (13.4)	
Medicare/ Medicaid	431 (42.3)	398 (42.6)	281 (40.0)	
Other insurance	449 (44.1)	404 (43.2)	328 (46.7)	
NIH Stroke Scale Score (IQR)	11 (6, 18)	12 (7, 19)	10 (6, 18)	0.023
NIH Stroke Scale Score				0.325
Score ≤ 7	288 (31.4)	257 (30.1)	218 (35.1)	
Score 8-12	230 (25.1)	204 (23.9)	144 (23.2)	
Score 13-18	176 (19.2)	180 (21.1)	128 (20.6)	
Score 19+	223 (24.3)	214 (25.0)	131 (21.1)	
Previous Medical History				
Hypertension Yes	752 (81.4)	691 (79.1)	528 (81.1)	0.414
Dyslipidemia Yes	346 (37.5)	332 (38.0)	261 (40.1)	0.548
CAD/prior MI Yes	210 (22.7)	232 (26.5)	164 (25.2)	0.165
Diabetes Yes	246 (26.6)	220 (25.2)	213 (32.7)	0.003
Smoking Yes	206 (22.3)	206 (23.6)	146 (22.4)	0.787
Atrial fibrillation/flutter Yes	159 (17.2)	197 (22.5)	119 (18.3)	0.012
Previous stroke Yes	166 (18.0)	168 (19.2)	148 (22.7)	0.059
Previous stroke or TIA Yes	74 (8.0)	85 (9.7)	69 (10.6)	0.191
Heart failure Yes	104 (11.3)	98 (11.2)	64 (9.8)	0.615

PVD Yes	25 (2.7)	33 (3.8)	21 (3.2)	0.439
Carotid stenosis Yes	14 (1.5)	18 (2.1)	14 (2.2)	0.583
No medical history	87 (8.6)	64 (6.8)	52 (7.4)	0.320
LKW (minutes) (IQR)	63 (42, 101)	65 (43, 94)	53 (33, 70)	<.0001
LKW (minutes)				<.0001
≤59	331 (33.3)	277 (30.3)	110 (16.6)	
60-85	217 (21.9)	244 (26.7)	158 (23.8)	
86+	445 (44.8)	392 (42.9)	395 (59.6)	
Time Part GCASR (days)				<.0001
≤738	66 (6.5)	74 (7.9)	92 (13.1)	
739-1133	115 (11.4)	128 (13.7)	107 (15.2)	
1134-1470	125 (12.4)	130 (13.9)	105 (14.9)	
1471+	705 (69.7)	606 (64.6)	399 (56.8)	
Hospital Location				0.011
Non-metropolitan	11 (1.1)	21 (2.2)	22 (3.1)	
Metropolitan	1,000 (98.9)	917 (97.8)	681 (96.9)	
Primary Stroke Center				<.0001
Yes	1006 (99.5)	924 (98.5)	680 (96.7)	
No	5 (0.5)	14 (1.5)	23 (3.3)	
Time of day				0.001
Day	695 (68.7)	591 (63.0)	426 (60.6)	
Night	316 (31.3)	347 (37.0)	277 (39.4)	
Hospital Size				<.0001
≤ 231 beds	98 (9.7)	154 (16.4)	114 (16.2)	
232-410 beds	253 (25.0)	237 (25.3)	241 (34.3)	
411+ beds	660 (65.3)	547 (58.3)	348 (49.5)	
Persistent or paroxysmal atrial fibrillation/flutter				0.027
	209 (20.7)	241 (25.8)	157 (22.4)	
Bleeding Complications[c]				0.022
Yes	38 (3.9)	51 (5.8)	46 (7.0)	

Abbreviations: tPA= tissue plasminogen activator; dtPA= door to tPA; GCASR=Georgia Coverdell Acute Stroke Registry; CL=Confidence limit; CAD=Coronary Artery Disease; MI=Myocardial Infarction; TIA= transient ischemic attack; PVD= Peripheral vascular disease; LKW=Last Known Well until Hospital Arrival Time; Time Part GCASR =Days Since Enrollment in GCASR to the Treatment of Patient

[a] Door to tPA time is categorized based on clinical relevance and cut points determined from data analysis.

[b] Chi-square and Wilcoxon tests were applied for nominal and quantitative variables, respectively.

[c] includes symptomatic intracranial hemorrhage <36 hours after tPA and serious systemic hemorrhage <36 hours

Table 2B: Door to tPA time by the patient outcomes readmission or death, GCASR 2008-2013

Outcome	≤60 min dtPA N(%)	61-90 min dtPA N(%)	≥91 min dtPA N(%)	p-value[a]
Readmission[b]				
Readmitted in 30 days	98 (26.2)	66 (14.9)	71 (21.5)	0.082
Death				
Death in 30 days	99 (26.5)	140 (31.6)	95 (28.8)	0.002
Death in 1-Year	177 (47.3)	237 (53.5)	164 (49.7)	<.0001

Abbreviations: tPA= tissue plasminogen activator; GCASR=Georgia Coverdell Acute Stroke Registry

[a] Chi-square test was applied

[b] Refers to readmitted within 30 days after discharge, and excludes those who died.

Table 3A: Relative risk[a] of 30-day readmission[b] by patient characteristics among IV tPA treated acute stroke patients discharged home, GCASR 2008-2013. Complete data.

Predictor	Odds ratio (95% CL)	p-value
Door to tPA (min)		0.575
≥ 91 min	1.37 (0.73, 2.59)	
61-90 min	1.04 (0.57, 1.87)	
≤60 min	Referent	
Gender		0.837
Female	0.95 (0.57, 1.58)	
Male	Referent	
Race		0.397
Blacks	0.98 (0.55, 1.75)	
Other	2.26 (0.67, 7.65)	
White	Referent	
Age (years)		0.733
76+	1.40 (0.59, 3.31)	
66-75	1.24 (0.54, 2.85)	
56-65	0.96 (0.46, 1.97)	
≤ 55	Referent	
Primary Insurance Source		0.381
No health insurance/self-pay	0.89 (0.42, 1.89)	
Medicare/ Medicaid	1.40 (0.79, 2.45)	
Other insurance	Referent	
NIH Stroke Scale Score		0.104
Score 19+	1.96 (0.93, 4.16)	
Score 13-18	1.32 (0.60, 2.87)	
Score 8-12	1.91 (1.09, 3.34)	
Score ≤ 7	Referent	
Previous Medical History		
Hypertension Yes	1.40 (0.69, 2.85)	0.337
Dyslipidemia Yes	0.94 (0.57, 1.58)	0.822
CAD/prior MI Yes	0.75 (0.41, 1.37)	0.332
Diabetes Yes	0.93 (0.54, 1.61)	0.795
Smoking Yes	1.04 (0.58, 1.87)	0.887
Atrial fib/flutter Yes	0.23 (0.07, 0.75)	0.017
Previous stroke Yes	3.77 (2.27, 6.27)	<.0001
Previous stroke or TIA Yes	1.77 (0.90, 3.49)	0.095
Heart failure Yes	1.61 (0.68, 3.83)	0.266
Carotid stenosis Yes	0.47 (0.06, 4.02)	0.463
LKW (minutes)		0.204
≤59	0.61 (0.35, 1.08)	
60-85	0.66 (0.34, 1.28)	

86+	Referent	
Time Since Enrollment in GCASR to Treatment of Patient (days)		0.091
≤738	0.46 (0.19, 1.09)	
739-1133	0.36 (0.13, 1.02)	
1134-1470	0.46 (0.17, 1.28)	
1471+	Referent	
Time of day		0.074
Day	1.68 (0.95, 2.98)	
Night	Referent	
Hospital Size		0.606
≤ 231 beds	1.52 (0.62, 3.71)	
232-410 beds	1.28 (0.58, 2.83)	
411+ beds	Referent	

Abbreviations: tPA= tissue plasminogen activator; GCASR=Georgia Coverdell Acute Stroke Registry; CL=Confidence limit; CAD=Coronary Artery Disease; MI=Myocardial Infarction; LWK=last known well until Hospital Arrival Time

[a]: Multivariable regression analysis was performed
[b] Refers to readmission within 30 days from discharge. N= 238

Table 3B: Relative risk[a] of 30-day readmission[b] by patient characteristics among IV tPA treated acute stroke patients discharged home, GCASR 2008-2013. Imputed data.

Predictor	Odds ratio (95% CL)	p-value
Door to tPA (min)		
≥ 91 min	1.20 (0.69, 2.11)	0.516
61-90 min	0.84 (0.48, 1.44)	0.520
≤60 min	Referent	
Gender		
Female	0.91 (0.58, 1.45)	0.697
Male	Referent	
Race		
Blacks	1.23 (0.74, 2.04)	0.424
Other	2.06 (0.67, 6.34)	0.206
White	Referent	
Age (years)		
76+	2.19 (0.98, 4.89)	0.056
66-75	1.80 (0.82, 3.94)	0.140
56-65	1.19 (0.61, 2.35)	0.610
≤ 55	Referent	
Primary Insurance Source		
No health insurance/self-pay	0.85 (0.43, 1.70)	0.650
Medicare/ Medicaid	1.16 (0.69, 1.93)	0.578
Other insurance	Referent	
NIH Stroke Scale Score		
Score 19+	1.90 (0.92, 3.93)	0.083
Score 13-18	1.80 (0.90, 3.60)	0.096
Score 8-12	1.62 (0.93, 2.83)	0.088
Score ≤ 7	Referent	
Previous Medical History		
Hypertension Yes	1.37 (0.72, 2.61)	0.336
Dyslipidemia Yes	0.70 (0.43, 1.14)	0.150
CAD/prior MI Yes	0.75 (0.42, 1.34)	0.332
Diabetes Yes	1.19 (0.71, 1.98)	0.511
Smoking Yes	1.08 (0.62, 1.88)	0.779
Atrial fib/flutter Yes	0.33 (0.13, 0.86)	0.023
Previous stroke Yes	3.77 (2.36, 6.01)	<.0001
Previous stroke or TIA Yes	1.57 (0.83, 2.99)	0.168
Heart failure Yes	1.58 (0.72, 3.43)	0.251
Carotid stenosis Yes	0.98 (0.22, 4.33)	0.982
LKW (minutes)		
≤59	0.74 (0.43, 1.27)	0.269
60-85	0.87 (0.47, 1.61)	0.656

86+	Referent	
Time Since Enrollment in GCASR to Treatment of Patient (days)		
≤738	0.71 (0.34, 1.45)	0.346
739-1133	0.52 (0.23, 1.21)	0.130
1134-1470	0.75 (0.33, 1.69)	0.491
1471+	Referent	
Time of day		
Day	1.77 (1.06, 2.96)	0.030
Night	Referent	
Hospital Size		
≤ 231 beds	1.48 (0.70, 3.13)	0.307
232-410 beds	1.30 (0.69, 2.42)	0.419
411+ beds	Referent	

Abbreviations: tPA= tissue plasminogen activator; GCASR=Georgia Coverdell Acute Stroke Registry; CL=Confidence limit; CAD=Coronary Artery Disease; MI=Myocardial Infarction; LWK=last known well until Hospital Arrival Time

[a]: Multivariable regression analysis was performed
[b] Refers to readmission within 30 days from discharge. N= 238

Table 3C: Relative risk[a] of 30-Day Mortality[b] by patient characteristics among IV tPA treated acute stroke patients, GCASR 2008-2013. Complete data.

Predictor	Odds ratio (95% CL)	p-value
Door to tPA (min)		0.037
≥ 91 min	1.28 (0.87-1.89)	
61-90 min	1.54 (1.11-2.15)	
≤60 min	Referent	
Gender		0.450
Female	0.90 (0.67-1.20)	
Male	Referent	
Race		0.797
Blacks	0.91 (0.65-1.29)	
Other	1.16 (0.48-2.82)	
White	Referent	
Age (years)		<.0001
76+	3.75 (1.97-7.13)	
66-75	2.13 (1.10-4.10)	
51-65	1.32 (0.71-2.46)	
≤ 50	Referent	
Primary Insurance Source		0.768
No health insurance/self-pay	1.01 (0.57-1.77)	
Medicare/ Medicaid	0.90 (0.66-1.22)	
Other insurance	Referent	
NIH Stroke Scale Score		<.0001
Score 19+	7.09 (4.44-11.32)	
Score 13-18	5.35 (3.29-8.71)	
Score 8-12	2.10 (1.23-3.56)	
Score ≤ 7	Referent	
Previous Medical History		
Hypertension Yes	1.16 (0.78-1.71)	0.458
Dyslipidemia Yes	0.76 (0.56-1.03)	0.077
CAD/prior MI Yes	1.03 (0.74-1.43)	0.868
Diabetes Yes	1.19 (0.86-1.64)	0.290
Smoking Yes	1.09 (0.72-1.67)	0.670
Atrial fib/flutter Yes	1.74 (1.25-2.41)	0.002
Previous stroke Yes	0.83 (0.57-1.20)	0.311
Previous stroke or TIA Yes	1.14 (0.70-1.84)	0.587
Heart failure Yes	1.25 (0.82-1.88)	0.288
Carotid stenosis Yes	0.58 (0.17-1.89)	0.344
No medical history	Referent	
LKW (minutes)		0.523
≤59	1.16 (0.82-1.64)	

60-85	1.24 (0.84-1.83)	
86+	Referent	
Time Since Enrollment in GCASR to Treatment of Patient (days)		0.818
≤738	0.94 (0.52-1.69)	
739-1133	0.89 (0.57-1.41)	
1134-1470	1.16 (0.76-1.77)	
1471+	Referent	
Time of day		0.223
Day	1.20 (0.89-1.62)	
Night	Referent	
Hospital Size		0.532
≤ 231 beds	0.93 (0.53-1.62)	
232-410 beds	1.23 (0.78-1.94)	
411+ beds	Referent	

Abbreviations: tPA= tissue plasminogen activator; GCASR=Georgia Coverdell Acute Stroke Registry; CL=Confidence limit; CAD=Coronary Artery Disease; MI=Myocardial Infarction; LWK=last known well until Hospital Arrival Time

[a]: Multivariable regression analysis was performed
[b] Refers to death within 30 days from admission. N=338

Table 3D: Relative risk[a] of 30-Day Mortality[b] by patient characteristics among IV tPA treated acute stroke patients, GCASR 2008-2013. Imputed data.

Predictor	Odds ratio (95% CL)	p-value
Door to tPA (min)		
≥ 91 min	1.60 (1.15-2.24)	0.006
61-90 min	1.57 (1.17-2.12)	0.003
≤60 min	Referent	
Gender		
Female	0.78 (0.61-1.01)	0.058
Male	Referent	
Race		
Blacks	0.88 (0.65-1.18)	0.385
Other	1.34 (0.66-2.72)	0.411
White	Referent	
Age (years)		
76+	3.93 (2.25-6.87)	<.0001
66-75	2.22 (1.26-3.94)	0.006
51-65	1.33 (0.77-2.29)	0.308
≤ 50	Referent	
Primary Insurance Source		
No health insurance/self-pay	0.97 (0.58-1.61)	0.910
Medicare/ Medicaid	0.97 (0.74-1.27)	0.818
Other insurance	Referent	
NIH Stroke Scale Score		
Score 19+	7.27 (4.76-11.11)	<.0001
Score 13-18	4.78 (3.08-7.42)	<.0001
Score 8-12	2.06 (1.27-3.34)	0.004
Score ≤ 7	Referent	
Previous Medical History		
Hypertension Yes	1.31 (0.92-1.85)	0.130
Dyslipidemia Yes	0.81 (0.62-1.05)	0.111
CAD/prior MI Yes	0.98 (0.74-1.31)	0.899
Diabetes Yes	1.22 (0.92-1.61)	0.172
Smoking Yes	1.02 (0.70-1.50)	0.900
Atrial fib/flutter Yes	1.60 (1.20-2.14)	0.001
Previous stroke Yes	0.83 (0.60-1.15)	0.259
Previous stroke or TIA Yes	1.08 (0.71-1.66)	0.714
Heart failure Yes	1.40 (0.98-2.01)	0.064
Carotid stenosis Yes	0.89 (0.35-2.26)	0.803
No medical history	Referent	
LKW (minutes)		
≤59	1.06 (0.78-1.44)	0.718

60-85	1.13 (0.80-1.59)	0.500
86+	Referent	
Time Since Enrollment in GCASR to Treatment of Patient (days)		
≤738	0.87 (0.54-1.42)	0.587
739-1133	0.78 (0.53-1.16)	0.220
1134-1470	1.11 (0.78-1.58)	0.557
1471+	Referent	
Time of day		
Day	1.12 (0.87-1.45)	0.375
Night	Referent	
Hospital Size		
≤ 231 beds	1.01 (0.63-1.62)	0.963
232-410 beds	1.13 (0.78-1.66)	0.516
411+ beds	Referent	

Abbreviations: tPA= tissue plasminogen activator; GCASR=Georgia Coverdell Acute Stroke Registry; CL=Confidence limit; CAD=Coronary Artery Disease; MI=Myocardial Infarction; LWK=last known well until Hospital Arrival Time

[a]: Multivariable regression analysis was performed
[b] Refers to death within 30 days from admission. N=338

Table 3E: Relative risk[a] of Death within 1 year[b] by patient characteristics among IV tPA treated acute stroke patients, GCASR 2008-2013. Complete data.

Predictor	Odds ratio (95% CL)	p-value
Door to tPA (min)		0.004
≥ 91 min	1.36 (0.99-1.88)	
61-90 min	1.61 (1.22-2.11)	
≤60 min	Referent	
Gender		0.948
Female	1.01 (0.79-1.29)	
Male	Referent	
Race		0.655
Blacks	1.14 (0.86-1.50)	
Other	1.05 (0.50-2.220	
White	Referent	
Age (years)		<.0001
76+	6.84 (3.94-11.87)	
66-75	3.26 (1.86-5.71)	
51-65	1.46 (0.85-2.50)	
≤ 50	Referent	
Primary Insurance Source		0.882
No health insurance/self-pay	1.08 (0.67-1.74)	
Medicare/ Medicaid	0.96 (0.74-1.24)	
Other insurance	Referent	
NIH Stroke Scale Score		<.0001
Score 19+	4.69 (3.33-6.60)	
Score 13-18	3.72 (2.60-5.34)	
Score 8-12	1.72 (1.18-2.50)	
Score ≤ 7	Referent	
Previous Medical History		
Hypertension Yes	1.29 (0.92-1.810	0.131
Dyslipidemia Yes	0.74 (0.58-0.96)	0.023
CAD/prior MI Yes	1.25 (0.94-1.64)	0.118
Diabetes Yes	1.17 (0.89-1.54)	0.249
Smoking Yes	1.00 (0.71-1.43)	0.983
Atrial fib/flutter Yes	1.37 (1.03-1.83)	0.034
Previous stroke Yes	0.90 (0.66-1.22)	0.481
Previous stroke or TIA Yes	0.97 (0.64-1.46)	0.873
Heart failure Yes	1.55 (1.08-2.22)	0.018
Carotid stenosis Yes	0.75 (0.30-1.88)	0.514
No medical history	Referent	
LKW (minutes)		0.510
≤59	0.85 (0.64-1.13)	

60-85	0.89 (0.64-1.23)	
86+	Referent	
Time Since Enrollment in GCASR to Treatment of Patient (days)		0.705
≤738	0.76 (0.47-1.24)	
739-1133	1.00 (0.69-1.45)	
1134-1470	1.05 (0.73-1.51)	
1471+	Referent	
Time of day		0.742
Day	1.04 (0.81-1.34)	
Night	Referent	
Hospital Size		0.976
≤ 231 beds	1.04 (0.72-1.51)	
232-410 beds	1.01 (0.75-1.36)	
411+ beds	Referent	

Abbreviations: tPA= tissue plasminogen activator; GCASR=Georgia Coverdell Acute Stroke Registry; CL=Confidence limit; CAD=Coronary Artery Disease; MI=Myocardial Infarction; LWK=last known well until Hospital Arrival Time

[a]: Multivariable regression analysis was performed
[b] Refers to death within 365 days from admission. N= 586

Table 3F: Relative risk[a] of Death within 1 year[b] by patient characteristics among IV tPA treated acute stroke patients, GCASR 2008-2013. Imputed data.

Predictor	Odds ratio (95% CL)	p-value
Door to tPA (min)		
≥ 91 min	1.69 (1.29-2.23)	0.0002
61-90 min	1.58 (1.23-2.02)	0.0003
≤60 min	Referent	
Gender		
Female	0.90 (0.73-1.12)	0.353
Male	Referent	
Race		
Blacks	1.15 (0.90-1.46)	0.259
Other	1.18 (0.64-2.19)	0.591
White	Referent	
Age (years)		
76+	7.86 (4.86-12.73)	<.0001
66-75	3.67 (2.25-5.99)	<.0001
51-65	1.66 (1.04-2.66)	0.033
≤ 50	Referent	
Primary Insurance Source		
No health insurance/self-pay	1.02 (0.67-1.57)	0.910
Medicare/ Medicaid	1.03 (0.82-1.30)	0.781
Other insurance	Referent	
NIH Stroke Scale Score		
Score 19+	4.70 (3.42-6.47)	<.0001
Score 13-18	3.32 (2.39-4.60)	<.0001
Score 8-12	1.68 (1.18-2.39)	0.004
Score ≤ 7	Referent	
Previous Medical History		
Hypertension Yes	1.31 (0.98-1.76)	0.073
Dyslipidemia Yes	0.78 (0.63-0.97)	0.029
CAD/prior MI Yes	1.18 (0.93-1.51)	0.170
Diabetes Yes	1.22 (0.96-1.55)	0.101
Smoking Yes	0.98 (0.72-1.34)	0.918
Atrial fib/flutter Yes	1.32 (1.02-1.69)	0.032
Previous stroke Yes	0.91 (0.70-1.19)	0.488
Previous stroke or TIA Yes	0.90 (0.62-1.29)	0.562
Heart failure Yes	1.70 (1.25-2.33)	0.001
Carotid stenosis Yes	0.89 (0.41-1.92)	0.758
No medical history	Referent	
LKW (minutes)		
≤59	0.86 (0.67-1.11)	0.254

60-85	0.90 (0.67-1.20)	0.457
86+	Referent	
Time Since Enrollment in GCASR to Treatment of Patient (days)		
≤738	0.80 (0.54-1.19)	0.271
739-1133	0.90 (0.65-1.24)	0.516
1134-1470	1.09 (0.81-1.47)	0.574
1471+	Referent	
Time of day		
Day	1.04 (0.84-1.29)	0.740
Night	Referent	
Hospital Size		
≤ 231 beds	1.08 (0.79-1.49)	0.630
232-410 beds	1.03 (0.80-1.32)	0.843
411+ beds	Referent	

Abbreviations: tPA= tissue plasminogen activator; GCASR=Georgia Coverdell Acute Stroke Registry; CL=Confidence limit; CAD=Coronary Artery Disease; MI=Myocardial Infarction; LWK=last known well until Hospital Arrival Time

[a]: Multivariable regression analysis was performed
[b] Refers to death within 365 days from admission. N= 586

Table 4: Door to tPA time association to readmission and mortality

	Readmission 30-day				Mortality 30-day				Mortality 1 year			
	Crude		Adjusted+		Crude		Adjusted+		Crude		Adjusted+	
Door to tPA time	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
0-60 min	Ref		Ref		Ref		Ref		Ref		Ref	
61-90 min	0.80	0.47, 1.38	1.05	0.58, 1.90	1.59	1.20, 2.10	1.36	0.95, 1.93	1.59	1.27, 1.98	1.45	1.08, 1.94
>90 min	1.22	0.72, 2.08	1.39	0.73, 2.63	1.43	1.05, 1.94	1.03	0.67, 1.58	1.43	1.12, 1.83	1.19	0.84, 1.68

+ Variables in the model: all variables listed in tables 3
Ref= reference

Appendix: Database Linkage accuracy [a]

Patient Characteristic	Listed for linkage N (%) or Median (IQR)	Linked with FRIL[b] N (%) or Median (IQR)
Total	3,233	2,898
Gender		
Male	1,605 (49.6)	1,427 (49.2)
Female	1,628 (50.4)	1,471 (50.8)
Race		
White	1,915 (59.3)	1,706 (58.9)
Black	1,209 (37.4)	1,100 (38.0)
Other	107 (3.3)	90 (3.1)
AGE	66 (55, 78))	67 (55, 78)
< 50 Years	525 (16.2)	479 (16.5)
50-65 Years	1,019 (31.5)	897 (30.9)
66-75 Years	669 (20.7)	590 (20.4)
76+ Years	1,020 (31.6)	932 (32.2)
Primary Insurance Source		
Medicare	1,154 (35.9)	1,039 (36.0)
Medicaid	149 (4.6)	139 (4.8)
Personal insurance only	823 (25.6)	736 (25.5)
Two or more sources	614 (19.1)	550 (19.1)
Self-pay/No Insurance	475 (14.8)	422 (14.6)
NIH Stroke Scale Score	11 (6, 18)	11 (6, 18)
Previous Medical History		
Hypertension	2,399 (80.1)	2,144 (79.9)
Dyslipidemia	1,142 (38.1)	1,021 (38.0)
Coronary artery disease/prior Myocardial Infarction	725 (24.2)	654 (24.4)
Smoking	735 (24.5)	666 (24.8)
Diabetes mellitus	841 (28.1)	746 (27.8)
Atrial fibrillation/flutter	550 (18.4)	502 (18.7)
Previous stroke	622 (20.8)	554 (20.6)
Heart failure	298 (9.9)	283 (10.5)
Peripheral vascular disease	91 (3.0)	86 (3.2)
Carotid stenosis	55 (1.8)	51 (1.9)
Prosthetic heart valve	33 (1.1)	28 (1.0)
Current pregnancy	2 (0.1)	1 (0.04)
Sickle Cell	1 (0.03)	1 (0.04)
No history of medical illness	236 (7.3)	214 (7.4)

Last Known Well to Hospital Arrival Time (minutes)	60 (40, 90	60 (40, 90)
Door-to-Needle Time (minutes)	69 (52, 93)	69 (52, 93)
Hospital Length of Stay (days)	5 (3, 8)	5 (3, 8)
Time Since Enrollment in GCASR to Treatment of Patient (days)	1,794 (1,190, 2,355)	1,813.5 (1,198, 2,369)
Discharge Disposition		
Home	1,513 (46.8)	1,350 (46.6)
Hospice - Home	45 (1.4)	44 (1.5)
Hospice - Health care facility	140 (4.3)	131 (4.5)
Acute care facility	86 (2.7)	71 (2.5)
Other health care facility	1,210 (37.4)	1,084 (37.4)
Expired	218 (6.7)	201 (6.9)
Left against medical advice	21 (0.7)	17 (0.6)
Hospital Location		
Non-metropolitan	76 (2.4)	72 (2.5)
Metropolitan	3,157 (97.7)	2,826 (97.5)
Primary Stroke Center Status		
No	72 (2.2)	67 (2.3)
Yes	3,161 (97.8)	2,831 (97.7)
Time of day		
Day	2,058 (63.9)	1,850 (64.1)
Night	1,161 (36.1)	1,036 (35.9)
Hospital Size		
< 101 beds	40 (1.2)	37 (1.3)
101-250 beds	423 (13.1)	397 (13.7)
251-400 beds	830 (25.7)	743 (25.6)
401+ beds	1,940 (60.0)	1,721 (59.39)

[a] Purpose of this table is to examine if the linkage procedure had any predilection for records of patients with specific characteristics. A small difference of one or two percent/IQR between the columns tells you that the merge between datasets was successful (i.e. probability of a successful merge between the two datasets did not depend on the characteristic examined).

[b] Linked with 87% sensitivity and an estimated specificity of 99.9%, via Fine-grained Records Integration and Linkage (FRIL) software(19, 20). The goal is to find similar percentages between those "listed for linkage" and those actually "linked with FRIL".