Title

Intravenous Tissue-Type Plasminogen Activator in Acute Ischemic Stroke Patients With History of Stroke Plus Diabetes Mellitus

Journal

Stroke, 50(6)

ISSN

0039-2499

Authors

Ehrlich, Matthew E
Liang, Li
Xu, Haolin
et al.

Publication Date

2019-06-01

DOI

10.1161/strokeaha.118.024172

Peer reviewed

Published in final edited form as:
Stroke. 2019 June ; 50(6): 1497–1503. doi:10.1161/STROKEAHA.118.024172.

Intravenous Tissue Plasminogen Activator in Acute Ischemic Stroke Patients with History of Prior Stroke Plus Diabetes

Matthew E. Ehrlich, MD, MPH, **Li Liang, PhD**, **Haolin Xu, MS**, **Andrzej S. Kosinski, PhD**, **Adrian F. Hernandez, MD, MS**, **Lee H. Schwamm, MD**, **Eric E. Smith, MD, MPH**, **Gregg C. Fonarow, MD**, **Deepak L. Bhatt, MD, MPH**, **Eric D. Peterson, MD, MPH**, and **Ying Xian, MD, PhD**

Department of Neurology, Duke University School of Medicine, Durham, NC (M.E.E.); Duke Clinical Research Institute, Durham, NC (L.L., H.X., A.S.K., A.F.H., E.D.P., Y.X.); Department of biostatistics and bioinformatics, Duke University School of Medicine, Durham, NC (A.S.K.); Department of Neurology, Institute for Heart, Vascular and Stroke Care, Massachusetts General Hospital and Harvard Medical School, Boston, MA (L.H.S.); Department of Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, Canada (E.E.S.); Division of Cardiology, Ronald Reagan University of California, Los Angeles Medical Center, Los Angeles, CA (G.C.F.); Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA (D.L.B.); Department of Medicine, Duke University School of Medicine, Durham, NC (E.D.P.)

Abstract

Background and Purpose—Acute ischemic stroke (AIS) patients with history of prior ischemic stroke plus concomitant diabetes mellitus (DM) were excluded from the ECASS III trial due to safety concerns. However, there are few data on use of intravenous tissue plasminogen activator (tPA) and symptomatic intracranial hemorrhage (sICH) or outcomes in this population.

Methods—Using data from the Get With The Guidelines-Stroke Registry (GWTG-Stroke) between February 2009 and September 2017 (n=1619 hospitals), we examined characteristics and outcomes among AIS patients treated with tPA within the 3–4.5 hour window who had a history of prior stroke and DM (HxS+DM, n=2129) versus those without either history (n=16,690).

Results—Compared with patients without either history, those with both prior stroke and DM treated with tPA after an acute ischemic stroke had a higher prevalence of cardiovascular risk factors in addition to history of prior stroke, diabetes, and more severe stroke (NIHSS median 8 [IQR 5–15] vs. 7 [4–13]). The unadjusted rates of sICH and in-hospital mortality were 4.3% (HxS +DM) vs 3.8% (without either history) (p=0.31) and 6.2% vs 5.5% (p=0.20), respectively. These differences were not statistically significant after risk adjustment (sICH, adjusted odds ratio [OR] 0.79[95% CI, 0.51–1.21], p=0.28; in-hospital mortality OR 0.77 [95% CI, 0.52–1.14], p=0.19). Unadjusted rate of functional independence (Modified Rankin Scale score [mRS] 0–2) at discharge was lower in those with history of prior stroke and DM (30.9% HxS+DM vs 44.8%

Corresponding Author:Matthew E Ehrlich, MD MPH, Duke University Medical Center, Dept. of Neurology, Box 3824, Durham, NC 27710, P: 919-684-3801, F: 919-613-3606, Matthew.ehrlich@duke.edu.

without either history, p=<0.0001), and this difference persisted after adjusting for baseline clinical factors (adjusted OR 0.76 [95% CI, 0.59–0.99], p=0.04).

Conclusion—Among AIS patients treated with intravenous tPA within the 3–4.5 hour window, history of prior stroke plus DM was not associated with statistically significant increased sICH or mortality risk.

Keywords

Acute Stroke; thrombolysis; tissue plasminogen activator; diabetes mellitus

Subject Terms

Ischemic Stroke; Complications; Quality and Outcomes; Diabetes Type 2

Background and Purpose

For acute ischemic stroke (AIS) patients, intravenous (IV) tissue plasminogen activator (tPA) remains the only effective medical treatment shown to improve outcomes[1–3]. However, many AIS patients do not receive this acute therapy due to the numerous exclusion criteria in the original pivotal trials of IV tPA, especially in the 3–4.5 hour window. History of prior stroke plus concomitant diabetes mellitus (HxS+DM), while no longer considered a contraindication in the most recent AHA/ASA guidelines[3], is considered a contraindication in European licensing for the drug. Unlike other contraindications to tPA, where high risk of bleeding and symptomatic intracerebral hemorrhage (sICH) is the major concern, the European licensing documentation for tPA also lists the basis for excluding patients with HxS+DM as due to a perceived less favorable benefit/risk ratio[4]. While randomized clinical trials represent the highest quality data, patients with HxS+DM were excluded from the ECASS III trial for IV tPA in the 3–4.5 hour window.[2] As of today, only 204 patients with HxS+DM were enrolled in all completed trials of tPA (NINDS A/B, ECASS I/II/III, ATLANTIS A/B, EPISTHET, IST-3).[5,6] These patients were either not treated in the 3–4.5 hours window or not evaluated for the effect of tPA in this specific subpopulation. Secondary analyses of trial data and observational studies have identified hyperglycemia or diabetes mellitus (DM) as a risk factor for sICH following thrombolytic therapy[7–11] as well as in untreated stroke[7,12,13]. However other studies have reported favorable outcomes with off-label IV tPA and have included patients with HxS+DM[14–19]. It has also been shown that these patients are being treated frequently in real-world practice, though limited to a relatively small sample[20].

We analyzed data from the Get With The Guidelines (GWTG)-Stroke database to compare characteristics, safety, and in-hospital outcomes among AIS patients treated with IV tPA in the 3- to 4.5 hour window who had HxS+DM versus those without either history.

Methods

The GWTG-Stroke program characteristics have been previously published.[21,22] This ongoing, voluntary national stroke registry and performance improvement program is

sponsored by the American Heart Association/American Stroke Association and was developed to improve the quality of care and outcomes for patients with acute ischemic stroke. Standardized data collection in the registry includes patient demographics, medical history (including history of prior stroke and DM), time of symptom onset and tPA administration, reasons for nontreatment with tPA, diagnostic testing and imaging, in-hospital treatment and outcomes (including symptomatic intracerebral hemorrhage [sICH; defined as a computed tomography <36 hours that shows ICH and physician's notes indicate clinical deterioration because of hemorrhage], hospital discharge destination, and ambulatory status at discharge). The validity and reliability of data collection in GWTG-Stroke has been previously reported[23]. The GWTG-Stroke program is sponsored by the AHA. IQVIA (Durham, NC) serves as the data collection and registry coordination center for GWTG-Stroke and the DCRI serves as the data analytical center for the GWTG. Institutional review board approval was granted to analyze aggregate, deidentified data for research purposes. The data set from this study is held securely in coded form at the DCRI. While data sharing agreements prohibit the AHA from making the data set publicly available, researchers may submit proposals for statistical analysis of the confidential data by the Duke Clinical Research Institute, with approval from the AHA. Details of the application process are available at http://www.heart.org/en/professional/quality-improvement/quality-research-and-publications/national-level-program-data-research-opportunities.

We included patients from GWTG-Stroke from February 2009 to October 2017 who were treated with IV tPA between 3- to 4.5 hours from symptom onset or last known well time, giving a study population of 34557patients from 1641 sites (Figure 1). We excluded patients who were already admitted to the hospital at the time of their stroke, received experimental IV tPA or catheter-based treatments, were treated with IV tPA at another hospital, transferred in from another hospital, or had missing data in medical history. An additional 10522 patients were excluded who had either prior stroke or DM but not both. After these exclusions, the study population included 29341 patients from 1619 hospitals. Among them, 2129 had HxS+DM, while 16,690 had history of neither prior stroke nor DM.

Baseline characteristics, comorbidities, and treating-hospital characteristics were described overall and by the patient groups of interest using proportions for categorical variables and medians with 25^{th} and 75^{th} percentiles for continuous variables. The standardized differences were used to compare these characteristics between the two patient groups. Unlike t-tests or chi-square tests, the standardized difference is not influenced by sample size. A standardized difference greater than 10 indicates a significant imbalance between the groups.[24]

Multivariable logistic regression modeling was then performed to evaluate the association between HxS+DM and in-hospital outcomes including sICH, in-hospital mortality, serious and life-threatening hemorrhage, modified Rankin Scale score (mRS) at discharge, ambulatory status and discharge disposition. The adjusted model controlled for baseline patient demographics, clinical factors, and hospital characteristics that are expected to be predictive of outcomes and have been used in prior GWTG-Stroke analyses to estimate tPA complications and in-hospital outcomes after stroke.[9,25] These variables included age, sex,

race (non-Hispanic white, non-Hispanic black, Hispanic, black, Asian, other), calendar year, medical history of atrial fibrillation/flutter, previous transient ischemic attack (TIA), coronary artery disease(CAD)/prior myocardial infarction (MI), carotid stenosis, peripheral vascular disease (PVD), hypertension, dyslipidemia, smoking, heart failure, arrival via emergency medical services (EMS), arrival during off hours (vs. regular hours, defined as 7AM-6PM Monday-Friday), National Institutes of Health Stroke Scale score (NIHSS), medications prior to admission including antiplatelet, anticoagulant, antihypertensive, cholesterol reducing agents and DM medications, vital signs and labs including body mass index (BMI), systolic blood pressure (SBP), blood glucose, serum creatinine, and international normalized ratio (INR). Hospital characteristics included academic status, geographic region, number of beds, annual ischemic stroke volume, annual IV tPA volume, Joint Commission primary stroke center status (PSC), comprehensive stroke center (CSC) status, and rural location. Generalized estimating equations were used in all regression models to account for within-hospital clustering. Patient data were missing for ≤5% on sex, race, EMS, NIHSS, antiplatelet, anticoagulation and cholesterol reducing medications prior to admission; other variables had larger percentage missing data as follows: antihypertensive medication (16%), diabetic medication (19%), SBP (9%), blood glucose (11%), INR (29%), BMI (35%), and serum creatinine (29%). Hospital variables were complete on geographic region, PSC, CSC, annual stroke volume, IV tPA volume. Data missing for number of beds, teaching status and rural location were ≤2%. Missing data, when small in number, were managed using simple imputation methods (medical histories, sex, race), whereas multiple imputation was used for other covariates.

All statistical analyses were performed by the Duke Clinical Research Institute using SAS software, version 9.4 (SAS Institute, Cary, NC). All p-values are 2-sided, and $p<0.05$ was considered statistically significant.

Results

The baseline characteristics of our study population are shown in Table 1. The two populations were generally similar in age and sex, however the patients with HxS+DM had higher prevalence of cardiovascular risk factors and all other co-morbidities examined, aside from atrial fibrillation and smoking. Median arrival NIHSS was one point higher in the HxS +DM group (8[5–15] vs 7[4–13]), and pre-admission independent ambulation was slightly less frequent in the HxS+DM group. As expected, antiplatelet use was more common in those with HxS+DM and arrival serum blood glucose was generally higher in those with HxS+DM compared to those with no history of DM or prior stroke.

The unadjusted rates of sICH and in-hospital mortality were 4.26% (HxS+DM) vs. 3.78% (without either history) (p=0.31) and 6.2% vs. 5.5% (p=0.20), respectively (Table 2). After multivariable logistic regression modeling adjusted for potential confounders, there was no statistically significant difference in the rates of sICH (OR 0.79, 95% CI [0.51–1.21], p=0.28), or in-hospital mortality (0.77, [0.52–1.14], p=0.19). The adjusted outcomes changed directionality, likely due to the higher cardiovascular risk profiles in those with HxS +DM. The absolute rates of systemic hemorrhage were <1% in each group and, after adjustment, patients with HxS+DM were less likely to experience life-threatening systemic

hemorrhage (0.82% vs. 0.77%, OR 0.25, [0.10–0.59], p=0.002). There was no difference in serious tPA complication rates (7.88% HxS+DM vs. 7.13% without either history, OR 0.76 [0.55, 1.05], p=0.099). There was a significant difference in discharge disposition, with patients with HxS+DM being slightly more likely to discharge to a skilled nursing facility (SNF), and less likely to discharge home, but no difference in discharge to inpatient acute rehabilitation facilities (IRF) after adjustment. In addition, those with HxS+DM were less likely to be able to ambulate independently at discharge (45.94% HxS+DM vs. 57.05% without either history, OR 0.77, [0.63–0.93], p=0.006) and less likely to be functionally independent, defined as mRS 0–2 (30.94% HxS+DM vs. 44.76% without either history, OR 0.76, [0.59–0.99], p=0.04).

Discussion

Using a large, contemporary registry of AIS patients we found that a combined history of prior stroke and concomitant DM was not associated with increased risk of sICH or death when treated with IV tPA in the 3–4.5 hour window, compared with healthier controls being treated for ischemic stroke in the same time window. However, patients with HxS+DM were less likely to be able to ambulate and function independently at discharge. These results endured after risk-adjustment for numerous clinical co-factors and potential confounders.

In a previous study using GWTG-Stroke data, we showed that patients meeting additional ECASS-III exclusion criteria for 3–4.5 hour treatment were nonetheless frequently treated with tPA, and that tPA-treated patients in this window with HxS+DM had rates of poor outcome and sICH that were no different compared with HxS+DM patients treated at 0–3 hours.[20]. However, in that paper we did not compare outcomes of patients with HxS+DM treated at 3–4.5 hours with other patients treated at 3–4.5 hours. Additionally, our prior paper reflected early experience with 3–4.5 treatment in routine clinical practice. This analysis, by contrast, compares patients who were treated within the 3–4.5 hour window with or without the ECASS-III exclusion of combined history of both prior stroke and DM, providing a comparison group with more similar treatment conditions, but more dissimilar patient characteristics. It also reflects more contemporary treatment practices and includes a much larger sample size.

In our study population, patients with HxS+DM had more severe strokes compared with the those without prior stroke and diabetes (median NIHSS 8 vs 7). Further, the HxS+DM group was more likely to have had higher presenting serum glucose measurements, which has a well established link to poor stroke outcomes[12,13,26–28]. The HxS+DM patients were also shown to have higher rates of almost all measured co-morbidities. In total, the HxS+DM group was far more medically complex than the relatively much healthier comparison group. Despite this, there was no difference in measured safety outcomes of sICH rates, in-hospital mortality, or serious tPA complications. The clinical outcome measure of functional independence, as defined by mRS of 0–2, was notably poorer in those with HxS+DM. While pre-index-stroke mRS scores were unavailable in the registry, this was not unexpected as patients in the HxS+DM group by definition have prior stroke which may have additional residual deficits and result in a higher mRS score at discharge.

Our findings are consistent with several prior observational studies[14,15,17–20,29]. These studies are generally much smaller and several compared ‘on-label’ vs ‘off-label’ usage of IV tPA more broadly, not specifically in the 3–4.5h window and with only a small number of patients with HxS+DM. All of the referenced studies showed no increased risk of sICH amongst those treated off label. Mishra et al.[16] specifically examined 1141 patients with HxS+DM, using the SITS-ISTR (Safe Implementation of Thrombolysis in Stroke – International Stroke Thrombolysis Register) registry for those treated with IV tPA and compared with a control group from a separate registry, VISTA (Virtual International Stroke Trials Archive). They found outcomes were in fact better in those with history of DM, history of stroke, and those with both histories when treated with IV tPA. Additionally, they found no interaction on outcome between prior stroke and DM with tPA treatment.

Further, patients with HxS+DM have not been specifically excluded in multiple prospective trials of thrombolysis in the 3–4.5 time frame. A 2009 meta-analysis[30] of patients treated with IV tPA in the 3–4.5 hour window showed increased chance of favorable outcome and no significant difference in mortality compared to placebo treated patients in all-comers. No sub-population analysis was completed to evaluate specifically those with HxS+DM, though only the 821 patients included from ECASS-III (50% of total analysis population) were enrolled under the tighter exclusion criteria of that trial. Similarly, the IST3 Clinical Trial[31] in 2013 did not exclude patients with HxS+DM, and showed long-term reduction in disability in those treated with IV tPA up to 6 hours from symptom onset.

Our study has limitations. First, despite being the largest nationwide stroke registry in US, participation in GWTG-Stroke is voluntary, therefore participating hospitals may not be representative of all US hospitals. Second, this was a retrospective observational analysis. Though robust attempts were made to control for variables which may introduce confounding or bias, unmeasured confounding and treatment selection bias may still exist. However, among measured potential confounders, presenting NIHSS and presentation serum glucose were higher in the HxS+DM group, which as previously noted, is associated with higher rates of sICH. Thus, it could be argued that if selection bias occurred, it is more likely to be against the HxS+DM patients’ chance of favorable outcome. Further, sICH was not centrally adjudicated and was based on locally interpreted imaging findings for individual patients within the database. The images themselves are not available within the GWTG-Stroke registry for review. Therefore, comparing rates of sICH with other studies is difficult, though our overall sICH rate (3.8%) is comparable to rates reported in other non-selected populations outside of randomized controlled trials[9,32–35]. Our data are not sufficient to show effectiveness of IV tPA in patients with HxS+DM, because this study is observational. Additionally, we were unable to evaluate or report long-term functional outcomes as those measures do not exist within the GWTG-Stroke registry. Our study was able to evaluate functional status (mRS) at discharge, discharge disposition, and ambulatory status at discharge, which have previously been shown to correlate with long-term functional outcomes at 90 days.[36]

In conclusion, among AIS patients treated with intravenous tPA within the 3–4.5 hour window, history of prior stroke plus DM was not associated with statistically significant increased sICH or mortality risk. These patients were excluded from ECASS-III based on

concern for increased risk of sICH or death and potential decreased benefit, therefore a reduced benefit/risk ratio. Given the long term benefit to treatment with IV tPA in stroke and no evidence of additional harm, it may be reasonable to consider thrombolytic treatment in the 3–4.5h window for patients with history of prior stroke and concomitant DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement:

This study was supported in part by grants from the American Heart Association (13CRP14410024 and 14SDG20460081) awarded to Dr. Xian. The Get With The Guidelines®–Stroke (GWTG-Stroke) program is provided by the American Heart Association/American Stroke Association. GWTG-Stroke is sponsored, in part, by Medtronic and has been funded in the past through support from Boeringher-Ingelheim, Merck, Bristol-Myers Squib/Sanofi Pharmaceutical Partnership, Janseen Pharmaceutical Companies of Johnson & Johnson and the AHA Pharmaceutical Roundtable.

Role of the Sponsor

The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author Disclosures:

ME Ehrlich: Dr. Ehrlich discloses modest research funding from Medtronic Foundation, Chiesi, Daiichi Sankyo Corp.

L Liang, H Xu: no disclosures

AS Kosinski: Dr. Kosinski discloses funding from the American Heart Association, modest.

F Hernandez: Dr. Hernandez discloses research funding from the American Heart association, AstraZeneca, GlaxoSmithKline, Merck, Luitpold, NHLBI, Novartis, PCORI, Verily; consulting for AstraZeneca, Bayer, Boston Scientific, Boehringer-Ingelheim, Merck, Novartis, Pfizer

LH Schwamm: Dr. Schwamm reports being the principal investigator of an investigator-initiated study of extended-window intravenous thrombolysis funded by the National Institutes of Neurological Disorders and Stroke (clinicaltrials.gov/show/NCT01282242) for which Genentech provided alteplase free of charge to Massachusetts General Hospital as well as supplemental per-patient payments to participating sites; serving as chair of the AHA/ASA GWTG stroke clinical work group and hospital accreditation Science Committee and Quality Oversight Committees, co-chair of Mission-Lifeline:Stroke; serving as a stroke systems consultant to the Massachusetts Department of Public Health; and serving as a scientific consultant to LifeImage regarding user interface design and usability, and regarding trial design and conduct to Lundbeck (international steering committee, DIAS3, 4 trial), Penumbra (data and safety monitoring committee, Separator 3D and MIND trials), NovoNordisk (data and safety monitoring committee, DeVOTE Trial), Genentech (Steering committee, TIMELESS trial) and Medtronic (Victory AF and Stroke AF trials).

GC Fonarow: Dr. Gregg C. Fonarow discloses the following relationships - Member of GWTG Steering Committee; Grant funding from Patient Centered Outcome Research Institute; Employee of the University of California which has a patent on an endovascular therapy device, Consultant: Janssen.

EE Smith: Dr. Smith has received consulting fees (modest) from Portola Pharmaceuticals and Alnylam Pharmaceuticals.

DL Bhatt: Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai

School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Fractyl, Merck, Novo Nordisk, PLx Pharma, Takeda.

ED Peterson: Dr. Peterson discloses research funding from Genentech.

Y Xian: Research grant to the Duke Clinical Research Institute from Genentech.

References

1. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue Plasminogen Activator for Acute Ischemic Stroke. N Engl J Med. 1995;333(24):1581–1588. doi: 10.1056/NEJM199512143332401 [PubMed: 7477192]
2. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–1329. [PubMed: 18815396]
3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye O, Bambakidis N, Becker K, et al. 2018 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. 2018;49:e46–e110 [PubMed: 29367334]
4. The European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products (CPMP) Summary Information on a Referral Opinion Following an Arbitration Pursuant to Article 29 of Directive 2001/83/EC, for Actilyse 11 2002.
5. Hacke W, Lyden P, Emberson J, Baignet C, Blackwell L, Albers G, et al. Effects of alteplase for acute stroke according to criteria defining the European Union and United States marketing authorizations: Individual-patient-data meta-analysis of randomized trials. Int J Stroke Off J Int Stroke Soc. 2018;13:175–189.
6. Emberson J, Lees KR, Lyden P, Balckwell L, Albers G, Bluhmki E, 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 Lond Engl. 2014;384:1929–1935.
7. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, et al. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. Neurology. 2002;59:669–674. [PubMed: 12221155]
8. Kase CS, Furlan AJ, Wechsler LR, Higashida RT, Rowley HA, Hart RG, et al. Cerebral hemorrhage after intra-arterial thrombolysis for ischemic stroke: the PROACT II trial. Neurology. 2001;57:1603–1610. [PubMed: 11706099]
9. Menon BK, Saver JL, Prabhakaran S, Reeves M, Liang L, Olson D, et al. Risk score for intracranial hemorrhage in patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator. Stroke. 2012;43:2293–2299. [PubMed: 22811458]
10. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Monting J, Schumacher M, et al. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. Cerebrovasc Dis Basel Switz. 2002;13:89–94.

11. Demchuk AM, Morgenstern LB, Krieger DW, Linda Chi T, Hu W, Wein TH, et al. Serum glucose level and diabetes predict tissue plasminogen activator-related intracerebral hemorrhage in acute ischemic stroke. Stroke. 1999;30:34–39. [PubMed: 9880385]
12. Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, et al. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. Neurology. 2002;59:67–71.. [PubMed: 12105309]
13. Gentile NT, Seftchick MW, Huynh T, Kruus LK, Gaughan J. Decreased mortality by normalizing blood glucose after acute ischemic stroke. Acad Emerg Med Off J Soc Acad Emerg Med. 2006;13:174–180.
14. Guillan M, Alonso-Canovas A, Garcia-Caldentey J, Sanchez-Gonzalez V, Hernandez-Medrano I, Defelipe-Mimbrera A, et al. Off-label intravenous thrombolysis in acute stroke. Eur J Neurol. 2012;19:390–394. [PubMed: 21895883]
15. Mishra NK, Ahmed N, Davalos A, Iversen HK, Melo T, Soinne L, et al. Thrombolysis outcomes in acute ischemic stroke patients with prior stroke and diabetes mellitus. Neurology. 2011;77:1866–1872. [PubMed: 22094479]
16. Mishra NK, Davis SM, Kaste M, Lees KR, VISTA Collaboration. Comparison of outcomes following thrombolytic therapy among patients with prior stroke and diabetes in the Virtual International Stroke Trials Archive (VISTA). Diabetes Care. 2010;33:2531–2537. [PubMed: 20843977]
17. Rubiera M, Ribo M, Santamarina E, Maisterra O, Delgado-Mederos R, Degado P, et al. Is it time to reassess the SITS-MOST criteria for thrombolysis?: A comparison of patients with and without SITS-MOST exclusion criteria. Stroke. 2009;40:2568–2571. [PubMed: 19423853]
18. Cronin CA, Shah N, Morovati T, Hermann LD, Sheth KN. No increased risk of symptomatic intracerebral hemorrhage after thrombolysis in patients with European Cooperative Acute Stroke Study (ECASS) exclusion criteria. Stroke. 2012;43:1684–1686. [PubMed: 22535272]
19. Frank B, Grotta JC, Alexandrov AV, Bluhmki E, Lyden P, Meretoja A, et al. Thrombolysis in stroke despite contraindications or warnings? Stroke. 2013;44:727–733. [PubMed: 23391774]
20. Cronin CA, Sheth KN, Zhao X, Messe S, Olson D, Hernandez A, et al. Adherence to Third European Cooperative Acute Stroke Study 3- to 4.5-Hour Exclusions and Association With Outcome: Data From Get With The Guidelines-Stroke. Stroke. 2014;45:2745–2749. [PubMed: 25104846]
21. Fonarow GC, Reeves MJ, Smith EE, Saver J, Zhao X, Olson D, et al. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. Circ Cardiovasc Qual Outcomes. 2010;3:291–302. [PubMed: 20177051]
22. Schwamm LH, Fonarow GC, Reeves MJ, Pan W, Frankel M, Smith EE, et al. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. Circulation. 2009;119:107–115. [PubMed: 19075103]
23. Xian Y, Fonarow GC, Reeves MJ, Webb L, Blevins J, Demyanenko VS, et al. Data quality in the American Heart Association Get With The Guidelines-Stroke (GWTG-Stroke): results from a national data validation audit. Am Heart J. 2012;163:392–398, 398.e1 [PubMed: 22424009]
24. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28:3083–3107. [PubMed: 19757444]
25. Smith EE, Shobha N, Dai D, Olson D, Reeves M, Saver J, et al. Risk score for in-hospital ischemic stroke mortality derived and validated within the Get With the Guidelines-Stroke Program. Circulation. 2010;122:1496–1504. [PubMed: 20876438]
26. de Courten-Myers GM, Kleinholz M, Wagner KR, Myers RE. Normoglycemia (not hypoglycemia) optimizes outcome from middle cerebral artery occlusion. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 1994;14:227–236.
27. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. Nat Rev Neurol. 2010;6:145–155. [PubMed: 20157308]

28. Ntaios G, Egli M, Faouzi M, Michel P. J-shaped association between serum glucose and functional outcome in acute ischemic stroke. Stroke. 2010;41:2366–2370. [PubMed: 20724712]

29. Meretoja A, Roine RO, Kaste M, Linna M, Roine S, Juntunen M, et al. Effectiveness of Primary and Comprehensive Stroke Centers PERFECT Stroke: A Nationwide Observational Study From Finland. Stroke. 2010;41:1102–1107. [PubMed: 20395609]

30. Lansberg MG, Bluhmki E, Thijs VN. Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: a metaanalysis. Stroke. 2009;40:2438–2441. [PubMed: 19478213]

31. IST-3 collaborative group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet Lond Engl. 2012;379:2352–2363.

32. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. Stroke. 2003;34:2847–2850. [PubMed: 14605319]

33. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet Lond Engl. 2007;369:275–282.

34. Xian Y, Federspiel JJ, Grau-Sepulveda M, Hernandez AF, Scwamm LH, Bhatt DL, et al. Risks and Benefits Associated With Prestroke Antiplatelet Therapy Among Patients With Acute Ischemic Stroke Treated With Intravenous Tissue Plasminogen Activator. JAMA Neurol. 2016;73:50–59. [PubMed: 26551916]

35. Goldstein JN, Marrero M, Masrur S, Pervez M, Barrocas AM, Abdullah A, et al. Management of thrombolysis-associated symptomatic intracerebral hemorrhage. Arch Neurol. 2010;67:965–969. [PubMed: 20697046]

36. Ovbiagele B, Saver JL. Day-90 acute ischemic stroke outcomes can be derived from early functional activity level. Cerebrovasc Dis Basel Switz. 2010;29:50–56

Health Research Alliance Author Manuscript

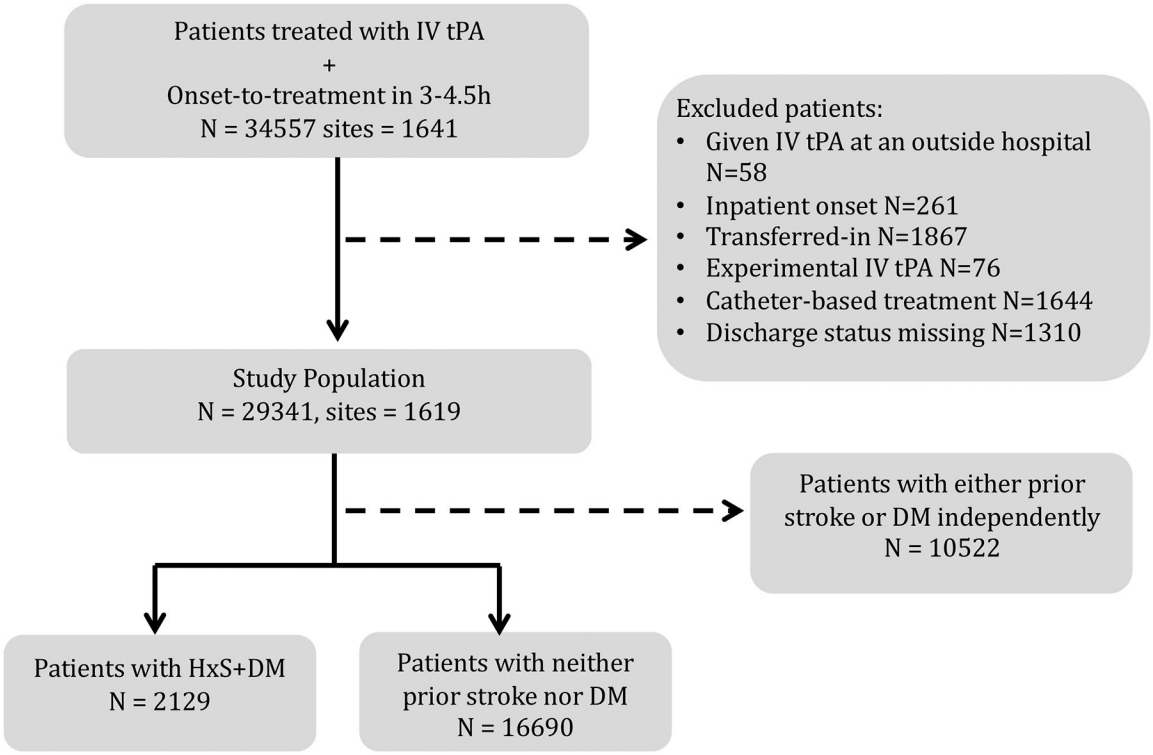

Figure 1.

IV tPA, intravenous tissue plasminogen activator; HxS+DM, History of stroke plus diabetes mellitus; DM, Diabetes mellitus. Dashed arrows indicate excluded patients; solid arrows indicate included patients.

Table 1.

Patient Demographic and Clinical Characteristics, And Treating Hospital Characteristics

	History of Stroke plus DMN=2129	No History of Stroke or DMN=16690	Std diff (%)
Age, median (SD)	69 (12.23)	68 (15.76)	8.63
Female sex, %	50.7	50.04	1.24
Race, % Non-Hispanic White Non-Hispanic Black Hispanic Asian Other	58.7 23.0 10.2 4.0 4.0	71.7 14.3 6.8 3.0 4.2	29.12
Medical history of:			
Atrial fibrillation, %	16.20	16.54	0.91
Prior TIA, %	13.76	6.87	22.80
CAD/MI, %	38.84	17.09	49.95
Carotid stenosis, %	5.50	1.55	21.55
PVD, %	7.37	2.52	22.51
Hypertension, %	87.74	64.21	57.30
Smoker, %	15.78	20.77	12.94
Dyslipidemia, %	59.09	34.54	50.77
Heart Failure, %	14.51	6.43	26.64
Obesity/overweight, %	21.42	13.21	21.82
Renal insufficiency, %	9.82	2.83	28.99
NIHSS, median (25–75%)	8 (5–15)	7 (4–13)	18.74
Ambulate independently prior to admission, %	87.13	95.65	34.0
Treatment Characteristics			
Arrival via EMS, %	74.61	73.14	3.35
Arrival during ‘off hours’ *, %	52.79	51.69	2.21
Onset to door, median (IQR)	131 (95–162)	136 (99–166)	8.10
Door to CT, minutes, median (IQR)	20 (12–32)	19 (11–32)	0.08
Onset to Needle, minutes, median (IQR)	211 (195–236)	214 (195–239)	7.50
Door to Needle, minutes, median (IQR)	80 (56–111)	75 (53–112)	4.72
Antiplatelet use, %	69.82	34.85	74.76
Anticoagulant use, %	7.44	4.15	14.10
Arrival SBP, mmHg, median (IQR)	158 (138–180)	155 (137–176)	9.51
Arrival DBP, mmHg, median (IQR)	84 (72–97)	86 (74–98)	9.04
Arrival Blood Glucose, mg/dL, median (IQR)	160 (121–225)	112 (99–131)	91.80
Hospital Characteristics			
Academic/teaching hospital, %	77.40	79.34	4.71
Geographic region West South Midwest Northeast	19.49 42.56 18.32 19.63	21.23 37.51 18.83 22.42	10.32
Primary Stroke Center, %	68.06	68.74	1.45

	History of Stroke plus DMN=2129	No History of Stroke or DMN=16690	Std diff (%)
Comprehensive Stroke Center, %	6.43	6.18	1.06
Annual ischemic stroke volume, median	243.02	244.18	0.05
Annual IV tPA cases, median	25.56	26.17	3.29

* Where normal hours defined as 7AM-6PM, Monday-Friday.

TIA, Transient ischemic attack; CAD, coronary artery disease; MI myocardial infarction; PVD, peripheral vascular disease; NIHSS, National Institutes of Health Stroke Scale; EMS, Emergency Medical Services; min, minutes; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Health Research Alliance Author Manuscript

Table 2.

Outcomes in Patients with History of Stroke Plus Diabetes Mellitus Treated with IV tPA in the 3–4.5 Hour Window

	History of Stroke Plus DMN=2129 (%)	No History of Stroke or DMN=16690 (%)	Unadjusted analysis		Adjusted Analysis	
			OR (95% CI)	P-value	OR (95% CI)	P-value
sICH	88/2068 (4.26)	614/16228 (3.78)	1.13 (0.90, 1.42)	0.31	0.79 (0.51, 1.21)	0.28
Life-Threatening Systemic Hemorrhage	17/2068 (0.82)	125/16228 (0.77)	1.07 (0.65, 1.75)	0.80	0.25 (0.10, 0.59)	0.002
Any Serious tPA Complication	163/2068 (7.88)	1157/16228 (7.13)	1.10 (0.94, 1.30)	0.2420	0.76 (0.55, 1.05)	0.0999
In-hospital Mortality	132/2129 (6.20)	916/16690 (5.49)	1.14 (0.94, 1.38)	0.20	0.77 (0.52, 1.14)	0.19
mRS 0–2	315/1918 (30.94)	3407/7611 (44.76)	0.56 (0.48, 0.64)	<0.001	0.76 (0.59, 0.99)	0.04
Ambulate Independently	792/1724 (45.94)	7666/13437 (57.05)	0.65 (0.59, 0.73)	<0.001	0.77 (0.63, 0.93)	0.006
Discharge to Hospice	107/2129 (5.03)	649/16690 (3.89)	1.31 (1.05, 1.63)	0.02	1.44 (0.94, 2.21)	0.09
Discharge SNF	401/2129 (18.84)	2096/16690 (12.56)	1.61 (1.42, 1.82)	<0.001	1.54 (1.23, 1.94)	<0.001
Discharge to Home	919/2129 (43.17)	8793/16690 (52.68)	0.69 (0.63, 0.75)	<0.001	0.89 (0.74, 1.07)	0.20

sICH, Symptomatic intracerebral hemorrhage; tPA, tissue plasminogen activator; mRS, modified Rankin Scale score; SNF, Skilled Nursing Facility