BMJ Open

Predictors and short term prognosis for stroke mimics treated with intravenous thrombolysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016311
Article Type:	Research
Date Submitted by the Author:	20-Feb-2017
Complete List of Authors:	Kostulas, Nikolaos; Karolinska Institutet, Clinical Science and Education Larsson, Martin Kall, Tor-Bjorn von Euler, Mia; Division of Clinical Pharmacology, Department of Laboratory Medicine Nathanson, David
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Ischemic stroke, Thrombolysis, Stroke mimic, SICH

Original article

Predictors and short term prognosis for stroke mimics treated with intravenous thrombolysis

Nikolaos Kostulas[1], Martin Larsson[1], Tor-Björn Käll[1†] Mia von Euler[1-2] and David Nathanson[1]

[1]Karolinska Institutet, Department of Clinical Science and Education, Sodersjukhuset, Stockholm, Sweden

[2]Karolinska Institutet Stroke Research Network at Södersjukhuset

† In memoriam

Key words: ischemic stroke, thrombolysis, stroke mimic, SICH

Short title: Stroke mimics receiving thrombolysis

Total words: 2377

Corresponding author:

Nikolaos Kostulas

Department of Internal Medicine,

Sjukhusbacken 10

Sodersjukhuset,

118 83 Stockholm, Sweden

Email: nikolaos.kostulas@gmail.com

Abstract

Objectives: Acute stroke management has changed dramatically over the recent years, where a timely assessment is driven by the expanding treatment options of acute ischemic stroke. This increases the risk in treating non-stroke patients (stroke mimics) with a possibly hazardous intravenous thrombolysis treatment (IVT).

Setting: Patients of the thrombolysis registry of Södersjukhuset AB, a secondary health center in Stockholm, were retrospectively studied to determine complications and outcome after IVT in strokes and stroke mimics.

Participants: Consecutively 674 recruited patients from January 1, 2008 to December 1, 2013 were analyzed regarding demographics and outcome at 3 months after onset of symptoms.

Results: Ischemic stroke was confirmed in 625 patients (93%), and 49 patients (7%) were stroke mimics. Patients with strokes were older than stroke mimics (72 versus 52 years, p<0.0001), and antihypertensive, and antithrombotic treatment were more common in stroke patients (p<0.0001 and p<0.01, respectively). NIHSS did not differ at time of presentation. Excellent outcome defined as modified Rankin Scale score 0-1, at 3 months, was less common in stroke than in stroke-mimics (45 versus 75%, p<0,0001). No stroke mimic had a symptomatic intracerebral hemorrhage. Age of less than 40 years was a strong predictor for a patient to be a stroke mimic (OR 10,3, p<0,0001).

Conclusions: Stroke mimics receiving IVT had a favorable outcome compared to stroke patients, and showed no hemorrhagic complications. Age below 40 years may be a predictor for stroke mimics.

Main strengths and limitations

- This paper is comprised of consecutive data over a large period of time, thus increasing sample size providing higher internal validity
- The work-up of stroke patients was done according to stroke guidelines also including follow-up by an experienced stroke doctor representing the natural setting in larger hospitals
- This is retrospective, single center study with external validity limitations
- The work-up at time did not include MRI in most patients, possibly explaining the relative low number of found stroke mimics

Introduction

The management of acute stroke has changed dramatically over the last years. The expansion of intravenous thrombolysis (IVT) given at most hospitals receiving stroke patients, as well as the continued drip and ship paradigm may increase the risk of erroneous assessment of the acute patient.[1,2] The struggle to decrease Door-to-Needle (DTN) time, might increase the risk of treating non-stroke patients even more. IVT comes with the risk of symptomatic intracerebral hemorrhage (SICH) that may differ between 2 to 9 % depending on the definition used.[3,4,5] It is well described that several disorders such as migraine, vertigo and seizures may appear with symptoms such as paresis, speech disturbance and visual loss and thereby mimic a stroke.[6,7] The proportion of stroke mimics in thrombolysis registries vary from 1 to 16%.[8-12] A retrospective single cohort study indicated that treating stroke mimics with IVT is safe.[13] Also, a multicenter cohort study showed only 1% of SICH in stroke mimics compared to 7,9% in ischemic stroke.[14] MRI-evaluation of the acute stroke patient may increase the chance of discriminating between a stroke mimic and an actual stroke,[15] However, this is limited by the availability of MRI scans in acute stroke. Scoring systems have been suggested to be used to differentiate between a stroke mimic and a stroke, and have been used in tele-stroke-networks.[16]

Here we retrospectively evaluated the outcome of IVT in a consecutive thrombolysis cohort of Södersjukhuset AB, in Stockholm, Sweden. Demographic and outcome variables were described in stroke and stroke mimics, and predictors of the latter were determined.

Materials and Methods

Patients were consecutively recruited at the Södersjukhuset AB, a large teaching hospital in an urban area of Stockholm. All stroke patients are seen by the internal medicine doctor on call with support during office hours by a neurologist and a stroke nurse in thrombolysis cases. Outside office hours a neurologist is available on call. Since January 2008 all patients receiving IVT have been prospectively followed up at 3 months and registered in a local thrombolysis registry. All patients receiving thrombolysis from January 1, 2008, to December 1, 2013 were retrospectively evaluated using the electronic and locally available thrombolysis database. All patient records were re-evaluated three months after sensor date (by DN) with regard to diagnosis and outcome after thrombolysis. Patients were described with regard to demographic parameters and laboratory parameters at admission and at follow-up at 3 months after onset of symptoms. Of 699 patients consecutively recruited in the thrombolysis registry, between Jan 2008 and Dec 2013, 674 were included in the final analysis. The study was approved by the regional ethical review board of Stockholm, EPN: 2012/626-31/4.

Data collection and Clinical variables

The evaluation of all patients at admission included collection of demographic data, medical history, vascular risk factors, National Institute of Health Stroke Scale (NIHSS) score upon admission, modified Rankin Scale score (mRS) before the ischemic event and biochemical test results. SICH was used according to the criteria of the National Institute of Neurological Disorders and Stroke trial ($SICH_{NINDS}$: any hemorrhage plus any

neurological deterioration).[3] Follow-up evaluation was performed at 3 months after IVT by a stroke nurse, and included clinical and functional evaluation by NIHSS, mRS, measurement of blood pressure (BP) and body temperature and laboratory tests. Information on date of death was available in electronic records for all deceased patients. Patients that had received IVT on more than one occasion (n=15) were included, but only the first time they received IVT was used in the final analysis.

Stroke mimics were determined using a set of clinical factors during hospital-stay and follow-up (by the responsible MD at discharge and by DN at follow up), and usually including repetitive dator-tomographic imaging according to clinical routine imaging after thrombolysis.

Stroke and Stroke mimics and Risk Factors

Ischemic stroke and transitory ischemic attacks (TIA) were classified according to ICD-10. Arterial hypertension (HT) was considered present when the patients were on antihypertensive treatment upon admission, or when HT was diagnosed by repeated measurements of systemic BP > 140/90mmHg during hospital stay. Diabetes mellitus (DM) was considered present when patients had a known diagnosis, and/or were on antidiabetic treatment upon admission. Hyperlipidemia was defined by the presence of statin treatment upon admission or fasting total-cholesterol $\geq$ 5.2 mmol/L or LDL-cholesterol $\geq$ 2.6 mmol/L. Atrial fibrillation was considered present when mentioned in patients' past medical history or present at admission ECG.

Data analysis

Normal distribution of the variables was tested with Shapiro-Wilk's test. Medians and interquartile ranges were used to describe the characteristics of the study participants. Differences in continuous variables among groups were investigated by the Mann-Whitney test, and categorical variables were analyzed using the χ^2 or Fishers exact test where appropriate. Logistic regression was used to investigate the associations between potential risk factors and outcome in stroke-mimic. Hosmer-Lemeshov goodness-of-fit test was used to examine whether the final multivariable models adequately fitted the data. Multiple tests correction has not been performed due to the exploratory purpose of the study. *P* values <0.05 were considered statistically significant. Analyses were done with SPSS version 20.0 (SPSS Inc. Chicago, IL).

Results

Stroke and Stroke mimic cohort

A total of 674 patients were included in the final analysis. Ischemic stroke was confirmed in 625 patients (93%) based on clinical and imaging data, and 48 patients (7%) were classified as stroke mimics after reviewing available clinical and imaging data.

Demographics, risk factors and clinical investigation profiles of the stroke and stroke mimic groups are presented in table 1. Patients with strokes were significantly older than stroke mimics (72 versus 54 years, p<0.0001), prior medication for HT (57% versus 28%, p<0.0001) and antithrombotic treatment (48% versus 28%, p=0.006) were more common in stroke patients. Hypertension was more common in stroke compared to stroke mimics (49% versus 25%, p=0.001) and serum creatinine was higher in stroke

(83 versus 75 µmol/L, p = 0.001) whereas DM, atrial fibrillation and hyperlipidemia did not differ between groups.

Stroke mimics

Stroke mimics were determined after retrospectively reviewing medical records. Of the 675 patients, 48 patients (7%) were diagnosed as a stroke mimic. Of the 48, 12 (25%) were determined functional with inorganic symptoms (functional mimics), 8 (17%) were due to epileptic seizures, 6 (12%) received symptom-diagnoses, 4 (8%) were diagnosed as alcohol intoxication, 3 (6%) with migraine, 3 (6%) with vertigo, 2 (4%) with Bell's palsy, 2 (4%) with hypotension, 2 (4%) with intracerebral tumor, 2 (4%) with visual loss, 1 (2%) with pain related paresis, 1 (2%) observational diagnosis, 1 (2%) eye muscle paresis, 1 (2%) ischemic heart disease and 1 (2%) headache .

Clinical outcome and safety characteristics

Baseline characteristics showed no differences in NIHSS between groups (Table 1), but at 24 hours NIHSS was higher in stroke than stroke mimics (2 versus 1, p=0.02, Table 2). There was no significant differences in SICH, 11 patients in the stroke group (2 %) suffered SICH and none of the stroke mimics. Extracerebral hemorrhage did not differ between groups either. Excellent outcome defined as mRS 0-1 at 3 months, was lower in stroke than in stroke mimics (45 versus 75 %, p<0.0001). Mortality at 3 months was higher in stroke than stroke mimics (12 versus 2 %, p<0.048)

Multivariate analysis of Predictors of Stroke mimics

In order to determine prognostic variables to predict a stroke mimic, risk factors and lab parameters showing a significant difference between stroke patients and stroke mimics (i.e. age less than 40 years, hypertension and plasma creatinine) were included in a logistic multivariable model (Table 3). In this model age below 40 years, adjusted for hypertension, atrial fibrillation and plasma creatinine, was significantly associated for being a stroke mimic (OR 8.7, p<0.0001). Hypertension and creatine levels were also found to be independent predictors for being a stroke mimic , whereas atrial fibrillation was not a predictor of a stroke mimic (Table 3).

Discussion

This retrospective analysis of thrombolysed patients over 6 years, in accordance with previous literature, show that stroke mimics are younger than stroke.[14,17] DTN times did not differ between groups, possibly indicating that standardized protocols were in place. Hemorrhagic complications post IVT did not differ in groups, which has been shown before.[3,18,19] Outcome measures such as NIHSS at 24 hours and mRS 0-1 at 3 months indicated a worse functional status in the stroke group and also showed, as expected, higher mortality among strokes than stroke mimics. Almost one fourth of the mimics were classified as functional mimics which is in line with other studies.[20] Using multivariate analysis, predictors of stroke mimics were assessed and age below 40 was found to be the strongest predictor for a patient to be a stroke mimic (OR 8.7, p<0.0001),

but also hypertension and creatinine levels (Table 3) could indicate a patient to be a stroke mimic. The TeleStroke Mimic-Score (TM-Score) can discriminate strokes versus stroke mimics and includes age as a continuous variable, comorbidities such as atrial fibrillation and hypertension and NIHSS>14.[16] However, the TM-Score may not be applicable in our stroke cohort due to lower NIHSS and the fact that we do not operate primarily within a tele-stroke-network. The mean NIHSS for thrombolysed stroke patients reported in the Swedish national quality register Riksstroke is 8.[21] Although, our numbers of stroke mimics was fairly low in comparison with current literature indicating that as high as 20 percent of all patients presenting as suspected strokes are mimics, further radiological work-up with MRI could arguably exclude a stroke mimic. MRI has a higher specificity (92%) for arterial ischemic stroke. A diffusion weighted imaging MRI protocol has been shown to discriminated stroke mimics from arterial strokes.[22-24] At our hospital the facilities did not at the time of the study allow rapid examination with MRI-imaging. The decrease in DTN times in recent years may also lead to higher frequencies of stroke mimics receiving thrombolysis, as could be shown in a single center study that found an association between decreasing DTN times and increased frequencies of stroke mimics receiving IVT.[25] This may warrant a better work-up of stroke presenting patients including the use of MRI. Moreover there is a need for future studies with greater sample sizes for evaluating risk scores to discriminate real stroke patients from stroke mimics. As previously described and showed also in our study, age is a potential variable to include in such scores.

Limitations

The first limitation is the retrospective character of our study. As a single center study the external validity may be limited. Although the internal validity is high as all follow up and data collection were carried out by two trained nurses and only one doctor reevaluated the medical records. To enhance the generalizabillity, we extended the study period and consequently the sample size. The work-up of the patients not undergoing an MRI increases the chance of missing out on stroke mimics, which can also explain the relatively low number of stroke mimics although other single cohort studies have shown similar or lower levels. However, at this time and even today most acute stroke work-up includes computer tomography, and stroke also remains a clinical diagnosis. Migraine aura might be visualized as a perfusion deficit on MRI and even though it has been reported to often involve several vascular territories it may still be mistaken as a stroke, even with the use of MRI.[26,27] At our center, the low number of stroke mimics may also be due to assessment by an experienced stroke neurologist at daytime. The stroke mimics showed a multitude of different diagnoses and from a larger sample one might be able to draw conclusions on more common stroke mimic diagnoses.

In conclusion, our retrospective cohort described relatively low numbers of stroke mimics, where low age may independently predict a patient to be a stroke mimic. Intravenous thrombolysis did not lead to significant complications in stroke mimics suggesting that when in doubt rt-PA should be given.

Contributorship statement

The authors thank Natalia Trezie and Linda Ekström, research nurses at the Department of Internal Medicine Södersjukhuset AB, who meticulously recruited all patients and performed all data collection. They thank Lina Benson (Karolinska Institutet, Department of Clinical Science and Education, Södersjukhuset, Stockholm) for excellent statistical advice.

Competing interests

The authors declare that no competing interests exist.

Funding

This study was supported by funds from Karolinska Institutet and the Fighting Stroke Project.

Data sharing statement

All authors agree on sharing data, none has been or is considered for publication elsewhere.

References

1. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.

2. Martin-Schild S, Morales MM, Khaja AM, Barreto AD, Hallevi H, Abraham A, Sline MR, Jones E, Grotta JC, Savitz SI. Is the drip-and-ship approach to delivering thrombolysis for acute ischemic stroke safe? J Emerg Med 2011;41:135-141.

3. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:581–1587.

4. The IST-3 collaborative group. 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*. 2012;379:2352–2363.

5. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.

6. Kidwell CS, Starkman S, Eckstein M, et al. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). Stroke 2000;31:71-76.

7. Yew KS, Cheng EM. Diagnosis of acute stroke. Am Fam Physician 2015;91:528-536.

8. Artto V, Putaala J, Strbian D, Meretoja A, Piironen K, Liebkind R, et al; Helsinki Stroke Thrombolysis Registry Group. Stroke mimics and intra- venous thrombolysis. *Ann Emerg Med*. 2012;59:27–32.

9. Tsivgoulis G, Alexandrov AV, Chang J, Sharma VK, Hoover SL, Lao AY, et al. Safety and outcomes of intravenous thrombolysis in stroke mimics: a 6-year, single-care center study and a pooled analysis of reported series. *Stroke*. 2011;42:1771–1774.

10. Uchino K, Massaro L, Hammer MD. Transient ischemic attack after tis- sue plasminogen activator: aborted stroke or unnecessary stroke therapy? *Cerebrovasc Dis*. 2010;29:57–61.

11. Winkler DT, Fluri F, Fuhr P, Wetzel SG, Lyrer PA, Ruegg S, et al. Thrombolysis in stroke mimics: frequency, clinical characteristics, and outcome. *Stroke*. 2009;40:1522–1525.

12. Chang J, Teleb M, Yang JP, Alderazi YJ, Chapple K, Frey JL et al. A model to prevent fibrinolysis in patients with stroke mimics. *J Stroke Cerebrovasc Dis* 2012;21:839–843.

13. Sivakumaran P, Gill D, Mahir G, Baheerathan A, Kar A. A retrospective cohort study on the use of intravenous thrombolysis in stroke mimics J Stroke Cerebrovasc Dis. 2016 May;25(5):1057-61

14. Zinkstok SM, Engelter ST, Gensicke H, Lyrer PA, Ringleb PA, Artto V, Putaala J, Haapaniemi E,

Tatlisumak T, Chen Y, Leys D, Sarikaya H, Michel P, Odier C, Berrouschot J, Arnold M, Heldner MR, Zini A, Fioravanti V, Padjen V, Beslac-Bumbasirevic L, Pezzini A, Roos YB, Nederkoorn PJ. Safety of thrombolysis in stroke mimics: results from a multicenter cohort study. *Stroke.* 2013 Apr;44(4):1080-4.

15. Albers GW. Expanding the window for thrombolytic therapy in acute stroke. The potential role of acute MRI for patient selection. Stroke 1999;30:2230-7.

16. Ali SF, Viswanathan A, Singhal AB, Rost NS, Forducey PG, Davis LW, Schindler J, Likosky W, Schlegel S, Solenski N, Schwamm LH; Partners Telestroke Network. The TeleStroke mimic (TM)-score: a prediction rule for identifying stroke mimics evaluated in a Telestroke Network. *J Am Heart Assoc.* 2014 Jun 23;3(3)

17. Chen Y, Bogosavljevic V, Leys D, et al. Intravenous throm- bolytic therapy in patients with stroke mimics: baseline characteristics and safety profile. Eur J Neurol 2011; 18:1246-1250.

18. The IST-3 collaborative group. 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*. 2012;379:2352–2363.

19. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.

20. Gargalas S, Weeks R, Khan-Bourne N, Shotbolt P, Simblett S, Ashraf L, Doyle C, Bancroft V, David AS. Incidence and outcome of functional stroke mimics admitted to a hyperacute stroke unit. *J Neurol Neurosurg Psychiatry.* 2015 Aug 28.

21. Riksstroke annual report 2014 and 2015. http://www.riksstroke.org/wp-content/uploads/2016/06/Riksstroke%C3%85rsrapport2015-PRELIMIN%C3%84R-WBB-%C3%A4ndrat-6-juli.pdf

22. Chernyshev OY, Martin-Schild S, Albright KC, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. Neurology 2010;74:1340—5.

23. Brazzelli M, Sandercock PA, Chappell FM, Celani MG, Righetti E, Arestis N, Wardlaw JM, Deeks JJ. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007424.

24. Eichel R, Hur TB, Gomori JM, Cohen JE, Leker RR. Use of DWI-only MR protocol for screening stroke mimics. J Neurol Sci. 2013 May 15;328(1-2):37-40.

25. Liberman AL, Liotta EM, Caprio FZ, Ruff I, Maas MB, Bernstein RA, Khare R, Bergman D, Prabhakaran S. Do efforts to decrease door-to-needle time risk increasing stroke mimic treatment rates? Neurol Clin Pract. 2015 Jun;5(3):247-252.

26. Floery D, Vosko MR, Fellner FA, Fellner C, Ginthoer C, Gruber F, Ransmayr G, Doerfler A, Uder M, Bradley WG. Acute-onset migrainous aura mimicking acute stroke: MR perfusion imaging features. AJNR Am J Neuroradiol. 2012 Sep;33(8):1546-52.

27. Förster A, Wenz H, Kerl HU, Brockmann MA, Groden C. Perfusion patterns in migraine with aura. Cephalalgia. 2014 Oct;34(11):870-6.

Table 1. Baseline characteristics of strokes and stroke mimics treated with IVT.

	Strokes		Stroke Mimics		
	No./Total	Median (IQR) or proportion	No./Total	Median (IQR) or proportion	*P* Value
Age, y	625	72 (64-81)	48	54 (40-67)	< 0.0001
Age ≤ 40 y	11/625	2%	12/48	25%	< 0.0001
Sex, female	290/626	46%	19/48	37.5%	0.3
Previous stroke or TIA	162/626	26%	12/48	25%	1.0
Hypertension	300/609	49%	12/48	25%	0.001
Diabetes mellitus	86/606	14%	5/47	11%	0.7
Hyperlipidemia	44/605	7%	2/47	4.3%	0.8
Atrial fibrillation	128/606	21%	4/47	8.5%	0.04
mRS 0-1 before stroke	556/626	89%	45/48	94%	0.5
NIHSS	548	6 (3-11)	47	5 (3-9)	0.8
Prior antihypertensive	357/626	57%	13/48	28%	< 0.0001
Prior antiplatelet/anticoagulant	301/625	48%	13/47	28%	0.006
Prior statin	155/626	25%	6/48	12.5%	0.06
Systolic blood pressure	575	155 (140-169)	47	144 (132-155)	0.04
Diastolic blood pressure	575	80 (70-90)	47	84 (79-96)	0.1
Door-needle time, min	619	58 (47-75)	48	56.5 (45-73)	1.0
Time stroke onset-rTPA, min	617	135 (104-180)	48	120 (91-191)	0.5
Serum glucose, mmol/L	562	6.5 (5.8-7.7)	43	6.1 (5.5-6.8)	0.1
Serum cholesterol, mmol/L	470	4.9 (4.3-5.8)	37	5.2 (4.6-5.8)	0.08
Serum LDL, mmol/L	456	2.9 (2.3-3.7)	36	3.1 (2.4-3.5)	0.3
Serum HDL , mmol/L	466	1.3 (1.1-1.6)	38	1.3 (1.1-1.7)	0.9
INR	575	1.0 (1.0-1.1)	47	1.0 (1.0-1.1)	1.0
Blood platelet count (*10^9/L)	583	224 (188-268)	47	226 (192-245)	0.9
Creatinin,μmol/L	580	83 (69-96)	45	75 (65-83)	0.001
High sensitive CRP	580	2 (1-6)	46	2 (0-4)	0.3
Adminstered dose rTPA, mg	599	67 (58-76)	45	68 (58-76)	0.9
BMI, kg· m^2	582	25 (23-28)	47	26 (21-29)	0.6

Table 2. Outcome and safety data after treatment with intravenous rTPA in strokes and stroke mimics

	Strokes		Stroke Mimics		
	No./Total	Median (IQR) or proportion	No./Total	Median (IQR) or proportion	*P* Value
SICH NINDS	11/542	2%	0/45	0%	1.0
mRS 0-1, 3 months	258/579	45%	35/47	75%	< 0.0001
Mortality, 3 months	69/595	12%	1/45	2%	0.048
Noncerebral complications (all)	27/562	5%	1/46	2%	0.7
-Extracerebral hemorrhage	16/562	3%	1/46	2%	NA
-Hypotension (< 90 mmHg)	2/562	0.3%	0/46	0%	NA
-Nausea	1/562	0.2%	0/50	0%	NA
-Allergic reactions	5/562	0.8%	0/50	0%	NA
Hospital stay, days	599	5 (3-8)	47	4 (2-7)	0.3
NIHSS 24 hours after rTPA	430	2 (0-6)	42	1 (0-2)	0.02

NA= not applicable

Table 3. Multivariable model with predictors of stroke mimics

Predictor	OR (95% CI)	*P* value
Age < 40	8.7 (3.2-24.0)	<0.0001
Hypertension	0.5 (0.2-0.99)	0.047
Atrial fibrillation	0.5 (0.2-1.5)	0.23
Plasma creatinine	0.9 (0.96-0.99)	0.01

STROBE Statement—checklist of items that should be included in reports of observational studies

	Page No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4, last pargraph	Explain the scientific background and rationale for the investigation being reported
Objectives	4, last paragraph	State specific objectives, including any prespecified hypotheses
Methods		
Study design	5	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
Variables	5-6	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	5-6	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	6	Describe any efforts to address potential sources of bias
Study size	5, last paragraph	Explain how the study size was arrived at
Quantitative variables	6	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	7, see data analysis	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	7*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	7*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	8*	*Cohort study*—Report numbers of outcome events or summary measures over time
Main results	7, Results first paragraph	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	9, see multivariate analysis	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	9, first paragraph Discussion	Summarise key results with reference to study objectives
Limitations	11	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	11	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	11	Discuss the generalisability (external validity) of the study results
Other information		
Funding	12	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Predictors and short term prognosis for stroke mimics treated with intravenous thrombolysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016311.R1
Article Type:	Research
Date Submitted by the Author:	29-May-2017
Complete List of Authors:	Kostulas, Nikolaos; Karolinska Institutet, Clinical Science and Education Larsson, Martin; Karolinska Institutet, Clinical Science and Education Kall, Tor-Bjorn von Euler, Mia; Division of Clinical Pharmacology, Department of Laboratory Medicine Nathanson, David; Karolinska Institutet, Clinical Science and Education
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Ischemic stroke, Thrombolysis, Stroke mimic, SICH

Original article

Predictors and short term prognosis for stroke mimics treated with intravenous thrombolysis

Nikolaos Kostulas[1], Martin Larsson[1], Tor-Björn Käll[1†] Mia von Euler[1-2] and David Nathanson[1]

[1]Karolinska Institutet, Department of Clinical Science and Education, Sodersjukhuset, Stockholm, Sweden

[2]Karolinska Institutet Stroke Research Network at Södersjukhuset

† In memoriam, deceased 2016-10-05

Key words: ischemic stroke, thrombolysis, stroke mimic, SICH

Short title: Stroke mimics receiving thrombolysis

Total words: 2443

Corresponding author:

Nikolaos Kostulas

Department of Internal Medicine,

Sjukhusbacken 10

Sodersjukhuset,

118 83 Stockholm, Sweden

Email: nikolaos.kostulas@gmail.com

Abstract

Objectives: Acute stroke management has changed dramatically over the recent years, where a timely assessment is driven by the expanding treatment options of acute ischemic stroke. This increases the risk in treating non-stroke patients (stroke mimics) with a possibly hazardous intravenous thrombolysis treatment (IVT).

Setting: Patients of the thrombolysis registry of Södersjukhuset AB, a secondary health center in Stockholm, were retrospectively studied to determine complications and outcome after IVT in strokes and stroke mimics.

Participants: Consecutively 674 recruited patients from January 1, 2008 to December 1, 2013 were analyzed regarding demographics and outcome at 3 months after onset of symptoms.

Results: Ischemic stroke was confirmed in 625 patients (93%), and 48 patients (7%) were stroke mimics. Patients with strokes were older than stroke mimics 72 (interquartile range: 64-81) versus 54 years (interquartile range 40-67), p<0.0001. Antihypertensive and antithrombotic treatment were more common in stroke patients (p<0.0001 and p=0.006, respectively). NIHSS did not differ at time of presentation. Excellent outcome defined as modified Rankin Scale score 0-1, at 3 months, was less common in stroke than in stroke-mimics (50 versus 87,5 %, p<0,0001). No stroke mimic had a symptomatic intracerebral hemorrhage. Age of less than 40 years may be a predictor for a patient to be a stroke mimic (OR:8.7, 95% CI: 3.2-24.0, p<0,0001).

Conclusions: Stroke mimics receiving IVT had a more favorable outcome compared to stroke patients, and showed no hemorrhagic complications. Age below 40 years may be a predictor for stroke mimics.

Main strengths and limitations

- This paper is comprised of consecutive data over a large period of time, thus increasing sample size providing higher internal validity
- The work-up of stroke patients was done according to stroke guidelines also including follow-up by an experienced stroke doctor representing the natural setting in larger hospitals
- This is retrospective, single center study with external validity limitations
- The work-up at time did not include MRI in most patients, possibly explaining the relative low number of found stroke mimics

Introduction

The management of acute stroke has changed dramatically over the last years. The expansion of intravenous thrombolysis (IVT) given at most hospitals receiving stroke patients, as well as the continued drip and ship paradigm may increase the risk of erroneous assessment of the acute patient.[1,2] The struggle to decrease Door-to-Needle (DTN) time, might increase the risk of treating non-stroke patients even more. IVT comes with the risk of symptomatic intracerebral hemorrhage (SICH) that may differ between 2 to 9 % depending on the definition used.[3,4,5] It is well described that several disorders such as migraine, vertigo and seizures may appear with symptoms such as paresis, speech disturbance and visual loss and thereby mimic a stroke.[6,7] The proportion of stroke mimics in thrombolysis registries vary from 1 to 16%[8-12]. In a meta-analysis of 9 prospective studies stroke mimicking patients were found to have a lower risk for intracerebral hemorrhage when compared to patients with true acute ischemic stroke (RR: 0.33, 95% CI: 0.14-0.77)[13] A retrospective single cohort study indicated that treating stroke mimics with IVT is safe. [14] Also, a multicenter cohort study showed only 1% of SICH in stroke mimics compared to 7,9% in ischemic stroke.[15] MRI-evaluation of the acute stroke patient may increase the chance of discriminating between a stroke mimic and an actual stroke,[16] However, this is not only limited by the availability of MRI scans in acute stroke, but also due to the time it takes to assess an patient with an MRI scan. Scoring systems have been suggested to be used to differentiate between a stroke mimic and a stroke, and have been used in tele-stroke-networks.[17]

Here we retrospectively evaluated the outcome of IVT in a consecutive thrombolysis cohort of Södersjukhuset AB, in Stockholm, Sweden. Demographic and outcome

variables were described in stroke and stroke mimics, and predictors of the latter were determined.

Materials and Methods

Patients were consecutively recruited at the Södersjukhuset AB, a large teaching hospital in an urban area of Stockholm. All stroke patients are primarily seen by the internal medicine doctor on call and during office hours also by a neurologist, who makes the final decision whether IVT will be given or not. Outside office hours a neurologist is available on call and supports the majority of all IVT cases. Since January 2008 all patients receiving IVT have been prospectively followed up at 3 months and registered in a local thrombolysis registry. All patients receiving thrombolysis from January 1, 2008, to December 1, 2013 were retrospectively evaluated using the electronic and locally available thrombolysis database. All patient records were re-evaluated three months after sensor date (by DN) with regard to diagnosis and outcome after thrombolysis. Patients were described with regard to demographic parameters and laboratory parameters at admission and at follow-up at 3 months after onset of symptoms. Of 699 patients consecutively recruited in the thrombolysis registry, between Jan 2008 and Dec 2013, 674 were included in the final analysis. The study was approved by the regional ethical review board of Stockholm, EPN: 2012/626-31/4.

Data collection and Clinical variables

The evaluation of all patients at admission included collection of demographic data, medical history, vascular risk factors, National Institute of Health Stroke Scale (NIHSS) score upon admission, modified Rankin Scale score (mRS) before the ischemic event and biochemical test results. SICH was used according to the criteria of the National Institute of Neurological Disorders and Stroke trial ($SICH_{NINDS}$: any hemorrhage plus any neurological deterioration).[3] Follow-up evaluation was performed at 3 months after IVT by a stroke nurse, and included clinical and functional evaluation by NIHSS, mRS, measurement of blood pressure (BP) and body temperature and laboratory tests. Information on date of death was available in electronic records for all deceased patients. Patients that had received IVT on more than one occasion (n=15) were included, but only the first time they received IVT was used in the final analysis.

Stroke mimics were determined using a set of clinical factors during hospital-stay and follow-up (by the responsible MD at discharge and by DN at follow up), and usually including repetitive computed-tomographic imaging according to clinical routine imaging after thrombolysis.

Stroke and Stroke mimics and Risk Factors

Ischemic stroke and transitory ischemic attacks (TIA) were classified according to ICD-10. Arterial hypertension (HT) was considered present when the patients were on antihypertensive treatment upon admission, or when HT was diagnosed by repeated measurements of systemic BP > 140/90mmHg during hospital stay. Diabetes mellitus (DM) was considered present when patients had a known diagnosis, and/or were on

antidiabetic treatment upon admission. Hyperlipidemia was defined by the presence of statin treatment upon admission or fasting total-cholesterol ≥ 5.2 mmol/L or LDL-cholesterol ≥ 2.6 mmol/L. Atrial fibrillation was considered present when mentioned in patients' past medical history or present at admission ECG.

Data analysis

Normal distribution of the variables was tested with Shapiro-Wilk's test. Medians and interquartile ranges were used to describe the characteristics of the study participants. Differences in continuous variables among groups were investigated by the Mann-Whitney test, and categorical variables were analyzed using the χ^2 or Fishers exact test where appropriate. Logistic regression was used to investigate the associations between potential risk factors and outcome in stroke-mimic. Hosmer-Lemeshov goodness-of-fit test was used to examine whether the final multivariable models adequately fitted the data. Multiple tests correction has not been performed due to the exploratory purpose of the study. *P* values <0.05 were considered statistically significant. Analyses were done with SPSS version 20.0 (SPSS Inc. Chicago, IL).

Results

Stroke and Stroke mimic cohort

A total of 674 patients were included in the final analysis, 25 patients were excluded due to previous treatment with IVT. Ischemic stroke was confirmed in 625 patients (93%)

based on clinical and imaging data, and 48 patients (7%) were classified as stroke mimics after reviewing available clinical and imaging data.

Demographics, risk factors and clinical investigation profiles of the stroke and stroke mimic groups are presented in table 1. Patients with strokes were significantly older than stroke mimics (72 (interquartile range: 64-81) versus 54 years (interquartile range 40-67), p<0.0001), prior medication for HT (57% versus 28%, p<0.0001) and antithrombotic treatment (48% versus 28%, p=0.006) were more common in stroke patients. Hypertension was more common in stroke compared to stroke mimics (49% versus 25%, p=0.001) and serum creatinine was higher in stroke (83 versus 75 µmol/L, p = 0.001) whereas DM, atrial fibrillation and hyperlipidemia did not differ between groups.

Stroke mimics

Stroke mimics were determined after retrospectively reviewing medical records. Of the 674 patients, 48 patients (7%) were diagnosed as a stroke mimic. Of the 48, 12 (25%) were determined functional with inorganic symptoms (functional mimics), 8 (17%) were due to epileptic seizures, 10 (21 %) received symptom-diagnoses (i.e. a descriptive diagnosis without a determined etiology) such as visual loss, eye muscle paresis, non-specific headache and paresis without cause, 4 (8%) were diagnosed as alcohol intoxication, 3 (6%) with migraine, 3 (6%) with vertigo, 2 (4%) with Bell's palsy, 2 (4%) with hypotension, 2 (4%) with intracerebral tumor, 1 (2%) with pain related paresis and 1 (2%) ischemic heart disease. Of the 48 stroke mimics 13 of 270 (4.8%) patients were treated during office time and 35 of 400 (8.8%) patients were treated during on call time. However on call time was not significantly associated to stroke mimicking neither in unadjusted (OR: 1.9, 95% CI: 0.9-3.6) nor in multivariable models (OR 1.8, 95% CI: 0.9-

3.7, Table 2).

Clinical outcome and safety characteristics

Baseline characteristics showed no differences in NIHSS between groups (Table 1), but at 24 hours NIHSS was higher in stroke than stroke mimics (2 versus 1, p=0.02, Table 3). There was no significant differences in SICH, 11 patients in the stroke group (2 %) suffered SICH and none of the stroke mimics. Extracerebral hemorrhage did not differ between groups either. Excellent outcome defined as mRS 0-1 at 3 months, was lower in stroke than in stroke mimics (50% versus 87.5 %, p<0.0001). Mortality at 3 months was higher in stroke than stroke mimics (12 versus 2 %, p<0.048)

Multivariate analysis of Predictors of Stroke mimics

In order to determine prognostic variables to predict a stroke mimic, risk factors and lab parameters showing a significant difference between stroke patients and stroke mimics (i.e. age less than 40 years, hypertension and plasma creatinine) were included in a logistic multivariable model (Table 2). In this model age below 40 years, adjusted for hypertension, atrial fibrillation and plasma creatinine, was significantly associated for being a stroke mimic (OR 8.7, p<0.0001). Hypertension and creatine levels were also found to be independent predictors for being a stroke mimic, whereas atrial fibrillation was not a predictor of a stroke mimic (Table 2).

Discussion

This retrospective analysis of thrombolysed patients over 6 years, in accordance with previous literature, show that stroke mimics are younger than stroke.[1518] DTN times did not differ between groups, possibly indicating that standardized protocols were in place. Hemorrhagic complications post IVT did not differ in groups, which has been shown before.[3,19,20] Outcome measures such as NIHSS at 24 hours and mRS 0-1 at 3 months indicated a worse functional status in the stroke group and also showed, as expected, higher mortality among strokes than stroke mimics. One fourth of the mimics were classified as functional mimics which is in line with other studies.[21] Using multivariate analysis, predictors of stroke mimics were assessed and age below 40 was found to be the strongest predictor for a patient to be a stroke mimic (OR 8.7, p<0.0001), but also hypertension and creatinine levels (Table 2) could indicate a patient to be a stroke mimic. The TeleStroke Mimic-Score (TM-Score) can discriminate strokes versus stroke mimics and includes age as a continuous variable, comorbidities such as atrial fibrillation and hypertension and NIHSS>14.[17] However, the TM-Score may not be applicable in our stroke cohort due to lower NIHSS and the fact that we do not operate primarily within a tele-stroke-network. Another potential risk factor for being a stroke mimic that were evaluated was the timepoint when admitted to hospital. We found a non significant relative risk for being a stroke mimic of 1.8 for patients admitted to hospital outside office hours. As the majority of the patients in the present cohort (59%) were admitted outside office hours it is not possible to infer that admission time is a true risk factor for stroke mimicking. Nevertheless, we cannot rule out that our sample size is too small for answering this question. As there were no neurologists present at hospital outside office

hours it seems prudent to believe that a presence of specialists in neurology during on call time may reduce the risk for treating stroke mimicking patients with IVT.

The mean NIHSS for thrombolysed stroke patients reported in the Swedish national quality register Riksstroke is 8.[22] Although, our numbers of stroke mimics was fairly low in comparison with current literature indicating that as high as 20 percent of all patients presenting as suspected strokes are mimics, further radiological work-up with MRI could arguably exclude a stroke mimic, but also indicate a stroke when considered a mimic. MRI has a higher specificity (92%) for arterial ischemic stroke. A diffusion weighted imaging MRI protocol has been shown to discriminated stroke mimics from arterial strokes.[23-25] At our hospital the facilities did not at the time of the study allow rapid examination with MRI-imaging. The decrease in DTN times in recent years may also lead to higher frequencies of stroke mimics receiving thrombolysis, as could be shown in a single center study that found an association between decreasing DTN times and increased frequencies of stroke mimics receiving IVT.[26] This may warrant a better work-up of stroke presenting patients including the use of MRI. Moreover there is a need for future studies with greater sample sizes for evaluating risk scores to discriminate real stroke patients from stroke mimics. As previously described and showed also in our study, age is a potential variable to include in such scores.

Limitations

The first limitation is the retrospective character of our study. As a single center study the external validity may be limited. Although the internal validity is high as all follow up and data collection were carried out by two trained nurses and only one doctor reevaluated the medical records. To enhance the generalizability, we extended the study period and consequently the sample size. The work-up of the patients not undergoing an MRI increases the chance of missing out on stroke mimics, which can also explain the relatively low number of stroke mimics although other single cohort studies have shown similar or lower levels. However, at this time and even today most acute stroke work-up includes computer tomography, and stroke also remains a clinical diagnosis. Migraine aura might be visualized as a perfusion deficit on MRI and even though it has been reported to often involve several vascular territories it may still be mistaken as a stroke, even with the use of MRI.[27, 28] At our center, the low number of stroke mimics may also be due to assessment by an experienced stroke neurologist at daytime. The stroke mimics showed a multitude of different diagnoses and from a larger sample one might be able to draw conclusions on more common stroke mimic diagnoses.

The finding of an overrepresentation of young patients (i.e. below 20 years of age) could reflect a higher likelihood to thrombolyse younger patients presenting with symptoms indicating a stroke. As the data is based on patients actually thrombolysed, the overrepresentation could be due to a higher willingness to thrombolyse rather than not thrombolyse in this age group if in doubt of the true diagnosis. Also, the likelihood of contraindication is lower in younger patients with less co-morbidity. Retrospective studies from Europe and USA have found advanced age together with stroke severity to

be the most common causes not to thrombolyse[29,30]

In conclusion, our retrospective cohort described relatively low numbers of stroke mimics, where low age may independently predict a patient to be a stroke mimic. Intravenous thrombolysis did not lead to significant complications in stroke mimics suggesting that the risk for IVT-associated complications in this group is low.

Contributorship statement

The authors thank Natalia Trezie and Linda Ekström, research nurses at the Department of Internal Medicine Södersjukhuset AB, who meticulously recruited all patients and performed all data collection. They thank Lina Benson (Karolinska Institutet, Department of Clinical Science and Education, Södersjukhuset, Stockholm) for excellent statistical advice.

Competing interests

The authors declare that no competing interests exist.

Funding

This study was supported by funds from Karolinska Institutet and the Fighting Stroke Project.

Data sharing statement

All authors agree on sharing data, none has been or is considered for publication elsewhere. Data available is that registered in the thrombolysis Registry of Södersjukhuset.

References

1. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.

2. Martin-Schild S, Morales MM, Khaja AM, Barreto AD, Hallevi H, Abraham A, Sline MR, Jones E, Grotta JC, Savitz SI. Is the drip-and-ship approach to delivering thrombolysis for acute ischemic stroke safe? J Emerg Med 2011;41:135-141.

3. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:581–1587.

4. The IST-3 collaborative group. 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*. 2012;379:2352–2363.

5. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.

6. Kidwell CS, Starkman S, Eckstein M, et al. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). Stroke 2000;31:71-76.

7. Yew KS, Cheng EM. Diagnosis of acute stroke. Am Fam Physician 2015;91:528-536.

8. Artto V, Putaala J, Strbian D, Meretoja A, Piironen K, Liebkind R, et al; Helsinki Stroke Thrombolysis Registry Group. Stroke mimics and intra- venous thrombolysis. *Ann Emerg Med*. 2012;59:27–32.

9. Tsivgoulis G, Alexandrov AV, Chang J, Sharma VK, Hoover SL, Lao AY, et al. Safety and outcomes of intravenous thrombolysis in stroke mimics: a 6-year, single-care center study and a pooled analysis of reported series. *Stroke*. 2011;42:1771–1774.

10. Uchino K, Massaro L, Hammer MD. Transient ischemic attack after tis- sue plasminogen activator: aborted stroke or unnecessary stroke therapy? *Cerebrovasc Dis*. 2010;29:57–61.

11. Winkler DT, Fluri F, Fuhr P, Wetzel SG, Lyrer PA, Ruegg S, et al. Thrombolysis in stroke mimics: frequency, clinical characteristics, and outcome. *Stroke*. 2009;40:1522–1525.

12. Chang J, Teleb M, Yang JP, Alderazi YJ, Chapple K, Frey JL et al. A model to prevent fibrinolysis in patients with stroke mimics. *J Stroke Cerebrovasc Dis* 2012;21:839–843.

13. Tsivgoulis G, Zand R, Katsanos A, Goyal N, Uchino K, Chang J et al. Safety of intravenous thrombolysis in stroke mimics: prospective 5-year study and comprehensive meta-analysis. *Stroke 2015;46:1281-1287.*

14. Sivakumaran P, Gill D, Mahir G, Baheerathan A, Kar A. A retrospective cohort study on the use of intravenous thrombolysis in stroke mimics J Stroke Cerebrovasc Dis. 2016 May;25(5):1057-61

15. Zinkstok SM, Engelter ST, Gensicke H, Lyrer PA, Ringleb PA, Artto V, Putaala J, Haapaniemi E, Tatlisumak T, Chen Y, Leys D, Sarikaya H, Michel P, Odier C, Berrouschot J, Arnold M, Heldner MR, Zini A, Fioravanti V, Padjen V, Beslac-Bumbasirevic L, Pezzini A, Roos YB, Nederkoorn PJ. Safety of thrombolysis in stroke mimics: results from a multicenter cohort study. *Stroke.* 2013 Apr;44(4):1080-4.

16. Albers GW. Expanding the window for thrombolytic therapy in acute stroke. The potential role of acute MRI for patient selection. Stroke 1999;30:2230-7.

17. Ali SF, Viswanathan A, Singhal AB, Rost NS, Forducey PG, Davis LW, Schindler J, Likosky W, Schlegel S, Solenski N, Schwamm LH; Partners Telestroke Network. The TeleStroke mimic (TM)-score: a prediction rule for identifying stroke mimics evaluated in a Telestroke Network. *J Am Heart Assoc.* 2014 Jun 23;3(3)

18. Chen Y, Bogosavljevic V, Leys D, et al. Intravenous throm- bolytic therapy in patients with stroke mimics: baseline characteristics and safety profile. Eur J Neurol 2011; 18:1246-1250.

19. The IST-3 collaborative group. 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*. 2012;379:2352–2363.

20. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.

21. Gargalas S, Weeks R, Khan-Bourne N, Shotbolt P, Simblett S, Ashraf L, Doyle C, Bancroft V, David AS. Incidence and outcome of functional stroke mimics admitted to a hyperacute stroke unit. *J Neurol Neurosurg Psychiatry.* 2015 Aug 28.

22. Riksstroke annual report 2014 and 2015. http://www.riksstroke.org/wp-content/uploads/2016/06/Riksstroke%C3%85rsrapport2015-PRELIMIN%C3%84R-WBB-%C3%A4ndrat-6-juli.pdf

23. Chernyshev OY, Martin-Schild S, Albright KC, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. Neurology 2010;74:1340—5.

24. Brazzelli M, Sandercock PA, Chappell FM, Celani MG, Righetti E, Arestis N, Wardlaw JM, Deeks JJ. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007424.

25. Eichel R, Hur TB, Gomori JM, Cohen JE, Leker RR. Use of DWI-only MR protocol for screening stroke mimics. J Neurol Sci. 2013 May 15;328(1-2):37-40.

26. Liberman AL, Liotta EM, Caprio FZ, Ruff I, Maas MB, Bernstein RA, Khare R, Bergman D, Prabhakaran S. Do efforts to decrease door-to-needle time risk increasing stroke mimic treatment rates? Neurol Clin Pract. 2015 Jun;5(3):247-252.

27. Floery D, Vosko MR, Fellner FA, Fellner C, Ginthoer C, Gruber F, Ransmayr G, Doerfler A, Uder M, Bradley WG. Acute-onset migrainous aura mimicking acute stroke: MR perfusion imaging features. AJNR Am J Neuroradiol. 2012 Sep;33(8):1546-52.

28. Förster A, Wenz H, Kerl HU, Brockmann MA, Groden C. Perfusion patterns in migraine with aura. Cephalalgia. 2014 Oct;34(11):870-6.

29. Reiff T, Michel P. Reasons and evolution of non-thrombolysis in acute ischaemic stroke. Emerg Med J. 2017 Apr;34(4):219-226

30. Cappellari M, Bosco M, Forlivesi S, Tomelleri G, Micheletti N, Carletti M, Bovi P. Reasons for exclusion from intravenous thrombolysis in stroke patients admitted to the Stroke Unit. J Thromb Thrombolysis. 2016 Nov;42(4):593-9.

Table 1. Baseline characteristics of strokes and stroke mimics treated with IVT.

	Strokes		Stroke Mimics		
	No./Total	Median (IQR) or proportion	No./Total	Median (IQR) or proportion	*P* Value
Age, y	625	72 (64-81)	48	54 (40-67)	< 0.0001
Age ≤ 40 y	11/625	2%	12/48	25%	< 0.0001
Sex, female	290/626	46%	19/48	37.5%	0.3
Previous stroke or TIA	162/626	26%	12/48	25%	1.0
Hypertension	300/609	49%	12/48	25%	0.001
Diabetes mellitus	86/606	14%	5/47	11%	0.7
Hyperlipidemia	44/605	7%	2/47	4.3%	0.8
Atrial fibrillation	128/606	21%	4/47	8.5%	0.04
mRS 0-1 before stroke	556/626	89%	45/48	94%	0.5
NIHSS	548	6 (3-11)	47	5 (3-9)	0.8
Prior antihypertensive	357/626	57%	13/48	28%	< 0.0001
Prior antiplatelet/anticoagulant	301/625	48%	13/47	28%	0.006
Prior statin	155/626	25%	6/48	12.5%	0.06
Systolic blood pressure	575	155 (140-169)	47	144 (132-155)	0.04
Diastolic blood pressure	575	80 (70-90)	47	84 (79-96)	0.1
Door-needle time, min	619	58 (47-75)	48	56.5 (45-73)	1.0
Time stroke onset-rTPA, min	617	135 (104-180)	48	120 (91-191)	0.5
Serum glucose, mmol/L	562	6.5 (5.8-7.7)	43	6.1 (5.5-6.8)	0.1
Serum cholesterol, mmol/L	470	4.9 (4.3-5.8)	37	5.2 (4.6-5.8)	0.08
Serum LDL, mmol/L	456	2.9 (2.3-3.7)	36	3.1 (2.4-3.5)	0.3
Serum HDL , mmol/L	466	1.3 (1.1-1.6)	38	1.3 (1.1-1.7)	0.9
INR	575	1.0 (1.0-1.1)	47	1.0 (1.0-1.1)	1.0
Blood platelet count (*10^9/L)	583	224 (188-268)	47	226 (192-245)	0.9
Creatinin,µmol/L	580	83 (69-96)	45	75 (65-83)	0.001
High sensitive CRP	580	2 (1-6)	46	2 (0-4)	0.3
Adminstered dose rTPA, mg	599	67 (58-76)	45	68 (58-76)	0.9
BMI, kg· m^2	582	25 (23-28)	47	26 (21-29)	0.6

Table 2. Multivariable model with predictors of stroke mimics

Predictor	OR (95% CI)	*P* value
Age < 40	8.7 (3.2-24.0)	<0.0001
Hypertension	0.5 (0.2-0.99)	0.047
On call time	1.8 (0.9-3.7)	0.09
Atrial fibrillation	0.5 (0.2-1.5)	0.2
Plasma creatinine (µmol/L)	0.9 (0.96-0.99)	0.01

Table 3. Outcome and safety data after treatment with intravenous rTPA in strokes and stroke mimics

	Strokes		Stroke Mimics		
	No./Total	Median (IQR) or proportion	No./Total	Median (IQR) or proportion	*P* Value
SICH NINDS	11/542	2%	0/45	0%	1.0
mRS 0-1, 3 months	258/513	50%	35/40	87.5%	< 0.0001
Mortality, 3 months	69/595	12%	1/45	2%	0.048
Noncerebral complications (all)	27/562	5%	1/46	2%	0.7
-Extracerebral hemorrhage	16/562	3%	1/46	2%	NA
-Hypotension (< 90 mmHg)	2/562	0.3%	0/46	0%	NA
-Nausea	1/562	0.2%	0/50	0%	NA
-Allergic reactions	5/562	0.8%	0/50	0%	NA
Hospital stay, days	599	5 (3-8)	47	4 (2-7)	0.3
NIHSS 24 hours after rTPA	430	2 (0-6)	42	1 (0-2)	0.02

NA= not applicable

STROBE Statement—checklist of items that should be included in reports of observational studies

	Page No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4, last pargraph	Explain the scientific background and rationale for the investigation being reported
Objectives	4, last paragraph	State specific objectives, including any prespecified hypotheses
Methods		
Study design	5	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
Variables	5-6	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	5-6	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	6	Describe any efforts to address potential sources of bias
Study size	5-6, last paragraph	Explain how the study size was arrived at
Quantitative variables	6	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	7, see data analysis	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	7*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	7*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	8*	*Cohort study*—Report numbers of outcome events or summary measures over time
Main results	7-8, Results first paragraph	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	9, see multivariate analysis	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	10, first paragraph Discussion	Summarise key results with reference to study objectives
Limitations	12	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	12	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	12	Discuss the generalisability (external validity) of the study results
Other information		
Funding	13	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Safety of thrombolysis in stroke mimics, an observational cohort study from an urban teaching hospital in Sweden

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016311.R2
Article Type:	Research
Date Submitted by the Author:	17-Aug-2017
Complete List of Authors:	Kostulas, Nikolaos; Karolinska Institutet, Clinical Science and Education Larsson, Martin; Karolinska Institutet, Clinical Science and Education Kall, Tor-Bjorn von Euler, Mia; Division of Clinical Pharmacology, Department of Laboratory Medicine Nathanson, David; Karolinska Institutet, Clinical Science and Education
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Ischemic stroke, Thrombolysis, Stroke mimic, SICH

Original article

Safety of thrombolysis in stroke mimics, an observational cohort study from an urban teaching hospital in Sweden

Nikolaos Kostulas[1], Martin Larsson[1], Tor-Björn Käll[1†] Mia von Euler[1-2] and David Nathanson[1]

[1]Karolinska Institutet, Department of Clinical Science and Education, Sodersjukhuset, Stockholm, Sweden

[2]Karolinska Institutet Stroke Research Network at Södersjukhuset

† In memoriam, deceased 2016-10-05

Key words: ischemic stroke, thrombolysis, stroke mimic, SICH

Short title: Stroke mimics receiving thrombolysis

Total words: 2443

Corresponding author:

Nikolaos Kostulas

Department of Internal Medicine,

Sjukhusbacken 10

Sodersjukhuset,

118 83 Stockholm, Sweden

Email: nikolaos.kostulas@gmail.com

Abstract

Objectives: Acute stroke management has changed dramatically over the recent years, where a timely assessment is driven by the expanding treatment options of acute ischemic stroke. This increases the risk in treating non-stroke patients (stroke mimics) with a possibly hazardous intravenous thrombolysis treatment (IVT).

Setting: Patients of the thrombolysis registry of Södersjukhuset AB, a secondary health center in Stockholm, were retrospectively studied to determine complications and outcome after IVT in strokes and stroke mimics.

Participants: Consecutively 674 recruited patients from January 1, 2008 to December 1, 2013 were analyzed regarding demographics and outcome at 3 months after onset of symptoms.

Results: Ischemic stroke was confirmed in 625 patients (93%), and 48 patients (7%) were stroke mimics. Patients with strokes were older than stroke mimics 72 (interquartile range: 64-81) versus 54 years (interquartile range 40-67), p<0.0001. Antihypertensive and antithrombotic treatment were more common in stroke patients (p<0.0001 and p=0.006, respectively). NIHSS did not differ at time of presentation. Excellent outcome defined as modified Rankin Scale score 0-1, at 3 months, was less common in stroke than in stroke-mimics (50 versus 87,5 %, p<0,0001). No stroke mimic had a symptomatic intracerebral hemorrhage. Age of less than 40 years may be a predictor for a patient to be a stroke mimic (OR:8.7, 95% CI: 3.2-24.0, p<0,0001).

Conclusions: Stroke mimics receiving IVT had a more favorable outcome compared to stroke patients, and showed no hemorrhagic complications. Age below 40 years may be a predictor for stroke mimics.

Main strengths and limitations

- This paper is comprised of consecutive data over a large period of time, thus increasing sample size providing higher internal validity
- The work-up of stroke patients was done according to stroke guidelines also including follow-up by an experienced stroke doctor representing the natural setting in larger hospitals
- This is retrospective, single center study with external validity limitations
- The work-up at time did not include MRI in most patients, possibly explaining the relative low number of found stroke mimics

Introduction

The management of acute stroke has changed dramatically over the last years. The expansion of intravenous thrombolysis (IVT) given at most hospitals receiving stroke patients, as well as the continued drip and ship paradigm may increase the risk of erroneous assessment of the acute patient.[1,2] The struggle to decrease Door-to-Needle (DTN) time, might increase the risk of treating non-stroke patients even more. IVT comes with the risk of symptomatic intracerebral hemorrhage (SICH) that may differ between 2 to 9 % depending on the definition used.[3,4,5] It is well described that several disorders such as migraine, vertigo and seizures may appear with symptoms such as paresis, speech disturbance and visual loss and thereby mimic a stroke.[6,7] The proportion of stroke mimics in thrombolysis registries vary from 1 to 16%[8-12]. In a meta-analysis of 9 prospective studies stroke mimicking patients were found to have a lower risk for intracerebral hemorrhage when compared to patients with true acute ischemic stroke (RR: 0.33, 95% CI: 0.14-0.77)[13] A retrospective single cohort study indicated that treating stroke mimics with IVT is safe. [14] Also, a multicenter cohort study showed only 1% of SICH in stroke mimics compared to 7,9% in ischemic stroke.[15] MRI-evaluation of the acute stroke patient may increase the chance of discriminating between a stroke mimic and an actual stroke,[16] However, this is not only limited by the availability of MRI scans in acute stroke, but also due to the time it takes to assess an patient with an MRI scan. Scoring systems have been suggested to be used to differentiate between a stroke mimic and a stroke, and have been used in tele-stroke-networks.[17]

Here we retrospectively evaluated the outcome of IVT in a consecutive thrombolysis

cohort of Södersjukhuset AB, in Stockholm, Sweden. Demographic and outcome variables were described in stroke and stroke mimics, and predictors of the latter were determined.

Materials and Methods

Patients were consecutively recruited at the Södersjukhuset AB, a large teaching hospital in an urban area of Stockholm. All stroke patients are primarily seen by the internal medicine doctor on call and during office hours also by a neurologist, who makes the final decision whether IVT will be given or not. Outside office hours a neurologist is available on call and supports the majority of all IVT cases. Since January 2008 all patients receiving IVT have been prospectively followed up at 3 months and registered in a local thrombolysis registry. All patients receiving thrombolysis from January 1, 2008, to December 1, 2013 were retrospectively evaluated using the electronic and locally available thrombolysis database. All patient records were re-evaluated three months after sensor date (by DN) with regard to diagnosis and outcome after thrombolysis. Patients were described with regard to demographic parameters and laboratory parameters at admission and at follow-up at 3 months after onset of symptoms. Of 699 patients consecutively recruited in the thrombolysis registry, between Jan 2008 and Dec 2013, 674 were included in the final analysis. The study was approved by the regional ethical review board of Stockholm, EPN: 2012/626-31/4.

Data collection and Clinical variables

The evaluation of all patients at admission included collection of demographic data, medical history, vascular risk factors, National Institute of Health Stroke Scale (NIHSS) score upon admission, modified Rankin Scale score (mRS) before the ischemic event and biochemical test results. SICH was used according to the criteria of the National Institute of Neurological Disorders and Stroke trial ($SICH_{NINDS}$: any hemorrhage plus any neurological deterioration).[3] Follow-up evaluation was performed at 3 months after IVT by a stroke nurse, and included clinical and functional evaluation by NIHSS, mRS, measurement of blood pressure (BP) and body temperature and laboratory tests. Information on date of death was available in electronic records for all deceased patients. Patients that had received IVT on more than one occasion (n=15) were included, but only the first time they received IVT was used in the final analysis.

Stroke mimics were determined using a set of clinical factors during hospital-stay and follow-up (by the responsible MD at discharge and by DN at follow up), and usually including repetitive computed-tomographic imaging according to clinical routine imaging after thrombolysis.

Stroke and Stroke mimics and Risk Factors

Ischemic stroke and transitory ischemic attacks (TIA) were classified according to ICD-10. Arterial hypertension (HT) was considered present when the patients were on antihypertensive treatment upon admission, or when HT was diagnosed by repeated measurements of systemic BP > 140/90mmHg during hospital stay. Diabetes mellitus

(DM) was considered present when patients had a known diagnosis, and/or were on antidiabetic treatment upon admission. Hyperlipidemia was defined by the presence of statin treatment upon admission or fasting total-cholesterol ≥ 5.2 mmol/L or LDL-cholesterol ≥ 2.6 mmol/L. Atrial fibrillation was considered present when mentioned in patients' past medical history or present at admission ECG.

Data analysis

Normal distribution of the variables was tested with Shapiro-Wilk's test. Medians and interquartile ranges were used to describe the characteristics of the study participants. Differences in continuous variables among groups were investigated by the Mann-Whitney test, and categorical variables were analyzed using the χ^2 or Fishers exact test where appropriate. Logistic regression was used to investigate the associations between potential risk factors and outcome in stroke-mimic. Hosmer-Lemeshov goodness-of-fit test was used to examine whether the final multivariable models adequately fitted the data. Multiple tests correction has not been performed due to the exploratory purpose of the study. *P* values <0.05 were considered statistically significant. Analyses were done with SPSS version 20.0 (SPSS Inc. Chicago, IL).

Results

Stroke and Stroke mimic cohort

A total of 674 patients were included in the final analysis, 25 patients were excluded due to previous treatment with IVT. Ischemic stroke was confirmed in 625 patients (93%)

based on clinical and imaging data, and 48 patients (7%) were classified as stroke mimics after reviewing available clinical and imaging data.

Demographics, risk factors and clinical investigation profiles of the stroke and stroke mimic groups are presented in **Table 1**.

Table 1. Baseline characteristics of strokes and stroke mimics treated with IVT.

	Strokes		Stroke Mimics		
	No./Total	Median (IQR) or proportion	No./Total	Median (IQR) or proportion	*P* Value
Age, y	625	72 (64-81)	48	54 (40-67)	< 0.0001
Age ≤ 40 y	11/625	2%	12/48	25%	< 0.0001
Sex, female	290/626	46%	19/48	37.5%	0.3
Previous stroke or TIA	162/626	26%	12/48	25%	1.0
Hypertension	300/609	49%	12/48	25%	0.001
Diabetes mellitus	86/606	14%	5/47	11%	0.7
Hyperlipidemia	44/605	7%	2/47	4.3%	0.8
Atrial fibrillation	128/606	21%	4/47	8.5%	0.04
mRS 0-1 before stroke	556/626	89%	45/48	94%	0.5
NIHSS	548	6 (3-11)	47	5 (3-9)	0.8
Prior antihypertensive	357/626	57%	13/48	28%	< 0.0001
Prior antiplatelet/anticoagulant	301/625	48%	13/47	28%	0.006
Prior statin	155/626	25%	6/48	12.5%	0.06
Systolic blood pressure	575	155 (140-169)	47	144 (132-155)	0.04
Diastolic blood pressure	575	80 (70-90)	47	84 (79-96)	0.1
Door-needle time, min	619	58 (47-75)	48	56.5 (45-73)	1.0
Time stroke onset-rTPA, min	617	135 (104-180)	48	120 (91-191)	0.5
Serum glucose, mmol/L	562	6.5 (5.8-7.7)	43	6.1 (5.5-6.8)	0.1
Serum cholesterol, mmol/L	470	4.9 (4.3-5.8)	37	5.2 (4.6-5.8)	0.08
Serum LDL, mmol/L	456	2.9 (2.3-3.7)	36	3.1 (2.4-3.5)	0.3
Serum HDL , mmol/L	466	1.3 (1.1-1.6)	38	1.3 (1.1-1.7)	0.9
INR	575	1.0 (1.0-1.1)	47	1.0 (1.0-1.1)	1.0
Blood platelet count (*10^9/L)	583	224 (188-268)	47	226 (192-245)	0.9
Creatinin,µmol/L	580	83 (69-96)	45	75 (65-83)	0.001
High sensitive CRP	580	2 (1-6)	46	2 (0-4)	0.3
Adminstered dose rTPA, mg	599	67 (58-76)	45	68 (58-76)	0.9
BMI, kg· m^2	582	25 (23-28)	47	26 (21-29)	0.6

Patients with strokes were significantly older than stroke mimics (72 (interquartile range: 64-81) versus 54 years (interquartile range 40-67), p<0.0001), prior medication for HT (57% versus 28%, p<0.0001) and antithrombotic treatment (48% versus 28%, p=0.006) were more common in stroke patients. Hypertension was more common in stroke compared to stroke mimics (49% versus 25%, p=0.001) and serum creatinine was higher in stroke (83 versus 75 µmol/L, p = 0.001) whereas DM, atrial fibrillation and hyperlipidemia did not differ between groups.

Stroke mimics

Stroke mimics were determined after retrospectively reviewing medical records. Of the 674 patients, 48 patients (7%) were diagnosed as a stroke mimic. Of the 48, 12 (25%) were determined functional with inorganic symptoms (functional mimics), 8 (17%) were due to epileptic seizures, 10 (21 %) received symptom-diagnoses (i.e. a descriptive diagnosis without a determined etiology) such as visual loss, eye muscle paresis, non-specific headache and paresis without cause, 4 (8%) were diagnosed as alcohol intoxication, 3 (6%) with migraine, 3 (6%) with vertigo, 2 (4%) with Bell's palsy, 2 (4%) with hypotension, 2 (4%) with intracerebral tumor, 1 (2%) with pain related paresis and 1 (2%) ischemic heart disease. Of the 48 stroke mimics 13 of 270 (4.8%) patients were treated during office time and 35 of 400 (8.8%) patients were treated during on call time. However on call time, was not significantly associated to stroke mimicking neither in unadjusted (OR: 1.9, 95% CI: 0.9-3.6) nor in multivariable models (OR 1.8, 95% CI: 0.9-3.7, **Table 2**).

Table 2. Outcome and safety data after treatment with intravenous rTPA in strokes and stroke mimics

	Strokes		Stroke Mimics		
	No./Total	Median (IQR) or proportion	No./Total	Median (IQR) or proportion	*P* Value
SICH $_{NINDS}$	11/542	2%	0/45	0%	1.0
mRS 0-1, 3 months	258/513	50%	35/40	87.5%	< 0.0001
Mortality, 3 months	69/595	12%	1/45	2%	0.048
Noncerebral complications (all)	27/562	5%	1/46	2%	0.7
-Extracerebral hemorrhage	16/562	3%	1/46	2%	NA
-Hypotension (< 90 mmHg)	2/562	0.3%	0/46	0%	NA
-Nausea	1/562	0.2%	0/50	0%	NA
-Allergic reactions	5/562	0.8%	0/50	0%	NA
Hospital stay, days	599	5 (3-8)	47	4 (2-7)	0.3
NIHSS 24 hours after rTPA	430	2 (0-6)	42	1 (0-2)	0.02

NA= not applicable

Clinical outcome and safety characteristics

Baseline characteristics showed no differences in NIHSS between groups **(Table 1),** but at 24 hours NIHSS was higher in stroke than stroke mimics (2 versus 1, p=0.02, **Table 2**). There was no significant differences in SICH, 11 patients in the stroke group (2 %)

suffered SICH and none of the stroke mimics. Extracerebral hemorrhage did not differ between groups either. Excellent outcome defined as mRS 0-1 at 3 months, was lower in stroke than in stroke mimics (50% versus 87.5 %, p<0.0001). Mortality at 3 months was higher in stroke than stroke mimics (12 versus 2 %, p<0.048)

Multivariate analysis of Predictors of Stroke mimics

In order to determine prognostic variables to predict a stroke mimic, risk factors and lab parameters showing a significant difference between stroke patients and stroke mimics (i.e. age less than 40 years, hypertension and plasma creatinine) were included in a logistic multivariable model **(Table 3).**

Table 3. Multivariable model with predictors of stroke mimics

Predictor	OR (95% CI)	*P* value
Age < 40	8.7 (3.2-24.0)	<0.0001
Hypertension	0.5 (0.2-0.99)	0.047
On call time	1.8 (0.9-3.7)	0.09
Atrial fibrillation	0.5 (0.2-1.5)	0.2
Plasma creatinine (µmol/L)	0.9 (0.96-0.99)	0.01

In this model age below 40 years, adjusted for hypertension, atrial fibrillation and plasma creatinine, was significantly associated for being a stroke mimic (OR 8.7, p<0.0001). Hypertension and creatine levels were also found to be independent predictors for being a stroke mimic, whereas atrial fibrillation was not a predictor of a stroke mimic **(Table 3).**

Discussion

This retrospective analysis of thrombolysed patients over 6 years, in accordance with previous literature, show that stroke mimics are younger than stroke.[1518] DTN times did not differ between groups, possibly indicating that standardized protocols were in place. Hemorrhagic complications post IVT did not differ in groups, which has been shown before.[3,19,20] Outcome measures such as NIHSS at 24 hours and mRS 0-1 at 3 months indicated a worse functional status in the stroke group and also showed, as expected, higher mortality among strokes than stroke mimics. One fourth of the mimics were classified as functional mimics which is in line with other studies.[21] Using multivariate analysis, predictors of stroke mimics were assessed and age below 40 was found to be the strongest predictor for a patient to be a stroke mimic (OR 8.7, p<0.0001), but also hypertension and creatinine levels **(Table 3)** could indicate a patient to be a stroke mimic. The TeleStroke Mimic-Score (TM-Score) can discriminate strokes versus stroke mimics and includes age as a continuous variable, comorbidities such as atrial fibrillation and hypertension and NIHSS>14.[17] However, the TM-Score may not be applicable in our stroke cohort due to lower NIHSS and the fact that we do not operate primarily within a tele-stroke-network. Another potential risk factor for being a stroke mimic that were evaluated was the timepoint when admitted to hospital. We found a non significant relative risk for being a stroke mimic of 1.8 for patients admitted to hospital outside office hours. As the majority of the patients in the present cohort (59%) were admitted outside office hours it is not possible to infer that admission time is a true risk factor for stroke

mimicking. Nevertheless, we cannot rule out that our sample size is too small for answering this question. As there were no neurologists present at hospital outside office hours it seems prudent to believe that a presence of specialists in neurology during on call time may reduce the risk for treating stroke mimicking patients with IVT.

The mean NIHSS for thrombolysed stroke patients reported in the Swedish national quality register Riksstroke is 8.[22] Although, our numbers of stroke mimics was fairly low in comparison with current literature indicating that as high as 20 percent of all patients presenting as suspected strokes are mimics, further radiological work-up with MRI could arguably exclude a stroke mimic, but also indicate a stroke when considered a mimic. MRI has a higher specificity (92%) for arterial ischemic stroke. A diffusion weighted imaging MRI protocol has been shown to discriminated stroke mimics from arterial strokes.[23-25] At our hospital the facilities did not at the time of the study allow rapid examination with MRI-imaging. The decrease in DTN times in recent years may also lead to higher frequencies of stroke mimics receiving thrombolysis, as could be shown in a single center study that found an association between decreasing DTN times and increased frequencies of stroke mimics receiving IVT.[26] This may warrant a better work-up of stroke presenting patients including the use of MRI. Moreover there is a need for future studies with greater sample sizes for evaluating risk scores to discriminate real stroke patients from stroke mimics. As previously described and showed also in our study, age is a potential variable to include in such scores.

Limitations

The first limitation is the retrospective character of our study. As a single center study the external validity may be limited. Although the internal validity is high as all follow up and data collection were carried out by two trained nurses and only one doctor reevaluated the medical records. To enhance the generalizability, we extended the study period and consequently the sample size. The work-up of the patients not undergoing an MRI increases the chance of missing out on stroke mimics, which can also explain the relatively low number of stroke mimics although other single cohort studies have shown similar or lower levels. However, at this time and even today most acute stroke work-up includes computer tomography, and stroke also remains a clinical diagnosis. Migraine aura might be visualized as a perfusion deficit on MRI and even though it has been reported to often involve several vascular territories it may still be mistaken as a stroke, even with the use of MRI.[27, 28] At our center, the low number of stroke mimics may also be due to assessment by an experienced stroke neurologist at daytime. The stroke mimics showed a multitude of different diagnoses and from a larger sample one might be able to draw conclusions on more common stroke mimic diagnoses.

The finding of an overrepresentation of young patients (i.e. below 40 years of age) could reflect a higher likelihood to thrombolyse younger patients presenting with symptoms indicating a stroke. As the data is based on patients actually thrombolysed, the overrepresentation could be due to a higher willingness to thrombolyse rather than not thrombolyse in this age group if in doubt of the true diagnosis. Also, the likelihood of contraindication is lower in younger patients with less co-morbidity. Retrospective studies from Europe and USA have found advanced age together with stroke severity to

be the most common causes not to thrombolyse[29,30]

In conclusion, our retrospective cohort described relatively low numbers of stroke mimics, where low age may independently predict a patient to be a stroke mimic. Intravenous thrombolysis did not lead to significant complications in stroke mimics suggesting that the risk for IVT-associated complications in this group is low.

Contributorship statement

The authors thank Natalia Trezie and Linda Ekström, research nurses at the Department of Internal Medicine Södersjukhuset AB, who meticulously recruited all patients and performed all data collection. They thank Lina Benson (Karolinska Institutet, Department of Clinical Science and Education, Södersjukhuset, Stockholm) for excellent statistical advice.

Competing interests

The authors declare that no competing interests exist.

Funding

This study was supported by funds from Karolinska Institutet and the Fighting Stroke Project.

Data sharing statement

All authors agree on sharing data, none has been or is considered for publication elsewhere. Data available is that registered in the thrombolysis Registry of Södersjukhuset.

References

1. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.

2. Martin-Schild S, Morales MM, Khaja AM, Barreto AD, Hallevi H, Abraham A, Sline MR, Jones E, Grotta JC, Savitz SI. Is the drip-and-ship approach to delivering thrombolysis for acute ischemic stroke safe? J Emerg Med 2011;41:135-141.

3. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:581–1587.

4. The IST-3 collaborative group. 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*. 2012;379:2352–2363.

5. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.

6. Kidwell CS, Starkman S, Eckstein M, et al. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). Stroke 2000;31:71-76.

7. Yew KS, Cheng EM. Diagnosis of acute stroke. Am Fam Physician 2015;91:528-536.

8. Artto V, Putaala J, Strbian D, Meretoja A, Piironen K, Liebkind R, et al; Helsinki Stroke Thrombolysis Registry Group. Stroke mimics and intra- venous thrombolysis. *Ann Emerg Med*. 2012;59:27–32.

9. Tsivgoulis G, Alexandrov AV, Chang J, Sharma VK, Hoover SL, Lao AY, et al. Safety and outcomes of intravenous thrombolysis in stroke mimics: a 6-year, single-care center study and a pooled analysis of reported series. *Stroke*. 2011;42:1771–1774.

10. Uchino K, Massaro L, Hammer MD. Transient ischemic attack after tis- sue plasminogen activator: aborted stroke or unnecessary stroke therapy? *Cerebrovasc Dis*. 2010;29:57–61.

11. Winkler DT, Fluri F, Fuhr P, Wetzel SG, Lyrer PA, Ruegg S, et al. Thrombolysis in stroke mimics: frequency, clinical characteristics, and outcome. *Stroke*. 2009;40:1522–1525.

12. Chang J, Teleb M, Yang JP, Alderazi YJ, Chapple K, Frey JL et al. A model to prevent fibrinolysis in patients with stroke mimics. *J Stroke Cerebrovasc Dis* 2012;21:839–843.

13. Tsivgoulis G, Zand R, Katsanos A, Goyal N, Uchino K, Chang J et al. Safety of intravenous thrombolysis in stroke mimics: prospective 5-year study and comprehensive meta-analysis. *Stroke 2015;46:1281-1287.*

14. Sivakumaran P, Gill D, Mahir G, Baheerathan A, Kar A. A retrospective cohort study on the use of intravenous thrombolysis in stroke mimics J Stroke Cerebrovasc Dis. 2016 May;25(5):1057-61

15. Zinkstok SM, Engelter ST, Gensicke H, Lyrer PA, Ringleb PA, Artto V, Putaala J, Haapaniemi E, Tatlisumak T, Chen Y, Leys D, Sarikaya H, Michel P, Odier C, Berrouschot J, Arnold M, Heldner MR, Zini A, Fioravanti V, Padjen V, Beslac-Bumbasirevic L, Pezzini A, Roos YB, Nederkoorn PJ. Safety of thrombolysis in stroke mimics: results from a multicenter cohort study. *Stroke.* 2013 Apr;44(4):1080-4.

16. Albers GW. Expanding the window for thrombolytic therapy in acute stroke. The potential role of acute MRI for patient selection. Stroke 1999;30:2230-7.

17. Ali SF, Viswanathan A, Singhal AB, Rost NS, Forducey PG, Davis LW, Schindler J, Likosky W, Schlegel S, Solenski N, Schwamm LH; Partners Telestroke Network. The TeleStroke mimic (TM)-score: a prediction rule for identifying stroke mimics evaluated in a Telestroke Network. *J Am Heart Assoc.* 2014 Jun 23;3(3)

18. Chen Y, Bogosavljevic V, Leys D, et al. Intravenous throm- bolytic therapy in patients with stroke mimics: baseline characteristics and safety profile. Eur J Neurol 2011; 18:1246-1250.

19. The IST-3 collaborative group. 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*. 2012;379:2352–2363.

20. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.

21. Gargalas S, Weeks R, Khan-Bourne N, Shotbolt P, Simblett S, Ashraf L, Doyle C, Bancroft V, David AS. Incidence and outcome of functional stroke mimics admitted to a hyperacute stroke unit. *J Neurol Neurosurg Psychiatry.* 2015 Aug 28.

22. Riksstroke annual report 2014 and 2015. http://www.riksstroke.org/wp-content/uploads/2016/06/Riksstroke%C3%85rsrapport2015-PRELIMIN%C3%84R-WBB-%C3%A4ndrat-6-juli.pdf

23. Chernyshev OY, Martin-Schild S, Albright KC, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. Neurology 2010;74:1340—5.

24. Brazzelli M, Sandercock PA, Chappell FM, Celani MG, Righetti E, Arestis N, Wardlaw JM, Deeks JJ. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007424.

25. Eichel R, Hur TB, Gomori JM, Cohen JE, Leker RR. Use of DWI-only MR protocol for screening stroke mimics. J Neurol Sci. 2013 May 15;328(1-2):37-40.

26. Liberman AL, Liotta EM, Caprio FZ, Ruff I, Maas MB, Bernstein RA, Khare R, Bergman D, Prabhakaran S. Do efforts to decrease door-to-needle time risk increasing stroke mimic treatment rates? Neurol Clin Pract. 2015 Jun;5(3):247-252.

27. Floery D, Vosko MR, Fellner FA, Fellner C, Ginthoer C, Gruber F, Ransmayr G, Doerfler A, Uder M, Bradley WG. Acute-onset migrainous aura mimicking acute stroke: MR perfusion imaging features. AJNR Am J Neuroradiol. 2012 Sep;33(8):1546-52.

28. Förster A, Wenz H, Kerl HU, Brockmann MA, Groden C. Perfusion patterns in migraine with aura. Cephalalgia. 2014 Oct;34(11):870-6.

29. Reiff T, Michel P. Reasons and evolution of non-thrombolysis in acute ischaemic stroke. Emerg Med J. 2017 Apr;34(4):219-226

30. Cappellari M, Bosco M, Forlivesi S, Tomelleri G, Micheletti N, Carletti M, Bovi P. Reasons for exclusion from intravenous thrombolysis in stroke patients admitted to the Stroke Unit. J Thromb Thrombolysis. 2016 Nov;42(4):593-9.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Page No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4, last pargraph	Explain the scientific background and rationale for the investigation being reported
Objectives	4, last paragraph	State specific objectives, including any prespecified hypotheses
Methods		
Study design	5	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
Variables	5-6	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	5-6	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	6	Describe any efforts to address potential sources of bias
Study size	5-6, last paragraph	Explain how the study size was arrived at
Quantitative variables	6	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	7, see data analysis	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	8*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	8*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	10*	*Cohort study*—Report numbers of outcome events or summary measures over time
Main results	7-10, Results first paragraph	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	11, see multivariate analysis	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	12, first paragraph Discussion	Summarise key results with reference to study objectives
Limitations	14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	14	Discuss the generalisability (external validity) of the study results
Other information		
Funding	15	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.