

## PEER REVIEW HISTORY

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## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Safety of thrombolysis in stroke mimics, an observational cohort study from an urban teaching hospital in Sweden
<b>AUTHORS</b>	Kostulas, Nikolaos; Larsson, Martin; Kall, Tor-Bjorn; von Euler, Mia; Nathanson, David

## VERSION 1 – REVIEW

<b>REVIEWER</b>	Blanca Fuentes Department of Neurology and Stroke Center. La Paz University Hospital
<b>REVIEW RETURNED</b>	05-Mar-2017

<b>GENERAL COMMENTS</b>	<p>This is a retrospective analysis of a cohort of patients treated with IVT in a single centre analysing the differences in outcomes between stroke patients and stroke mimics as well as the possible predictive factors for the diagnosis of stroke mimic. This study has some methodological limitations and unfortunately, in this current version, it doesn't add any novelty to current knowledge on this topic.</p> <ul style="list-style-type: none"><li>• The main limitations like the retrospective character and being a single centre study have been acknowledged by the authors. But other important limitation is that patients were primarily attended by the internal medicine doctor and not by a neurologist. This fact could have influence in the decision of treating some of the stroke mimics that could be more easily identified as such if they had been attended by a neurologist at the first time. It should be interesting to know whether stroke mimics were more frequent at outside office hours. Have you analysed this issue?</li><li>• A study addressing outcome of stroke mimics after IVT should include a cohort of stroke mimics not treated with IVT, as the interesting question is not whether IVT-treated stroke mimics have better outcomes than IVT-stroke patients but whether IVT-treated stroke mimics have or not similar outcomes than non IVT-treated stroke mimics, i.e the real safety of IVT treatment in stroke mimics. In this sense, I am quite surprised to read that up to 25% of stroke mimics in this IVT-cohort were dead or dependent at 3 months and one stroke-mimic patient had an extracerebral haemorrhage related to IVT. For this reason, in my opinion, the conclusion that "when in doubt rt-PA should be given" is too strong and not supported by the findings in this study.</li><li>• We should be cautious when suggesting that patients under 40 years have higher odds to be a stroke mimics, as although the</li></ul>
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	<p>proportion of those patients in the stroke group is small (2%), the absolute number is similar to that of the mimics group (11 vs. 12).</p> <ul style="list-style-type: none"> <li>• Other comments: <ul style="list-style-type: none"> <li>o A total of 699 patients were recruited in the thrombolysis registry but only 674 were included in final analysis. Please, clarify the reason of excluding 25 patients.</li> <li>o Please, clarify what do you mean with "Symptom-diagnoses" and "observational diagnosis"</li> <li>o In table 1 it is reported that up to 25% of stroke mimics had a previous stroke or TIA. Do they really were prior stroke/TIA or could they be also stroke mimics? In addition, 15 patients received IVT on more than one occasion. Do any stroke mimic receive IVT more than once?</li> </ul> </li> </ul>
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<b>REVIEWER</b>	Georgios Tsivgoulis National and Kapodistrian University of Athens
<b>REVIEW RETURNED</b>	11-Mar-2017

<b>GENERAL COMMENTS</b>	<p>The present study represents a retrospective cohort analysis on the complications and outcomes of IVT for acute ischemic stroke patients and stroke mimics admitted to a secondary health center. The study is of potential interest, however several points should be taken into consideration:</p> <ul style="list-style-type: none"> <li>- abstract: "(72 versus 52 years)". The authors should also provide the corresponding standard deviations</li> <li>- abstract: "(OR 10,3, p&lt;0,0001)". The authors should also provide the corresponding confidence intervals</li> <li>- abstract: "Stroke mimics receiving IVT had a favorable outcome" could be better rephrased to "Stroke mimics receiving IVT had a more favorable outcome"</li> <li>- Introduction: "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". It is not only a matter of limited availability, brain MRI may be time-consuming and thus delay prompt IVT treatment.</li> <li>- Introduction: The authors should also cite a very recent meta-analysis on the safety of intravenous thrombolysis in stroke mimics (Stroke. 2015;46:1281-7)</li> <li>- "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." It should be clearly stated by the authors who is responsible for IVT administration in their institution: the internist, the neurologist or the emergency doctor? If the neurologist is available only during office hours, who is in charge for AIS patients eligible for IVT presenting out of office hours?</li> <li>- "dator-tomographic imaging". Do authors mean "computed-tomography imaging"?</li> </ul>
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	<p>- Some of the final diagnoses reported by the authors (eg. Bell's palsy) are not difficult to differentiate from an acute ischemic stroke by an experienced neurologist. Some other final diagnoses are vague (eg. headache, symptom-diagnoses, observational diagnoses). The authors should further elucidate the aforementioned stroke mimic categories.</p> <p>- "The work-up of the patients not undergoing an MRI increases the chance of missing out on stroke mimics". This is not entirely true. MRI could also reveal true stroke cases considered and incorrectly classified as mimics.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Blanca Fuentes

Institution and Country: Department of Neurology and Stroke Center. La Paz University Hospital

This is a retrospective analysis of a cohort of patients treated with IVT in a single centre analysing the differences in outcomes between stroke patients and stroke mimics as well as the possible predictive factors for the diagnosis of stroke mimic. This study has some methodological limitations and unfortunately, in this current version, it doesn't add any novelty to current knowledge on this topic.

Comment 1 & 2

1: The main limitations like the retrospective character and being a single centre study have been acknowledged by the authors. But other important limitation is that patients were primarily attended by the internal medicine doctor and not by a neurologist. This fact could have influence in the decision of treating some of the stroke mimics that could be more easily identified as such if they had been attended by a neurologist at the first time.

Reply: We apologize for not having properly clarified the process of decision making according to allocation to rTPA treatment. At Södersjukhuset all IVT treatment decisions during office hours are made by a neurologist. During non-office hours the decisions are supported by a neurologist on call. This is now clarified at page 5, line 5-8 and at page 4 line 1-3 we have added: 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 IVT cases.

2: It should be interesting to know whether stroke mimics were more frequent at outside office hours. Have you analyzed this issue?

Reply: This is an important remark. After analyzing this issue we found a numerical difference of treating Stroke mimics during office hours versus "on call hours". In fact the relative risk for being a stroke mimic treated during on call time was 1.8. However this difference was not statistically significant ( $p=0.09$ ). We therefore added in the result section, page 8, line 18-22: 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 3). In the discussion, p 10, line 17-23, section we added: 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 during on call time 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 during on call time it seems prudent to infer that a presence of specialists in neurology during on call time may reduce the risk for treating stroke mimicking patients with IVT.

### Comment 3

A study addressing outcome of stroke mimics after IVT should include a cohort of stroke mimics not treated with IVT, as the interesting question is not whether IVT-treated stroke mimics have better outcomes than IVT-stroke patients but whether IVT-treated stroke mimics have or not similar outcomes than non IVT-treated stroke mimics, i.e the real safety of IVT treatment in stroke mimics. In this sense, I am quite surprised to read that up to 25% of stroke mimics in this IVT-cohort were dead or dependent at 3 months and one stroke-mimic patient had an extracerebral haemorrhage related to IVT. For this reason, in my opinion, the conclusion that “when in doubt rt-PA should be given” is too strong and not supported by the findings in this study.

Reply: Thanks for the comment, it is of great importance. Firstly, the mortality in the stroke-mimic group were extremely low as only one patient died (and the death was not associated to IVT-treatment in this case) during the follow up. Moreover it is difficult to make any inferences about the frequency of hemorrhagic complications due to IVT as only one patient experienced a non-fatal extra cerebral bleeding. When evaluating the NIHSS after IVT it decreased from 5 to 2 (median), that is further supporting the assumption that stroke mimics does not suffer from severe complications from IVT. However, your comment on mRS 3 months after IVT forced us to reevaluate our source-data. After reevaluation and recalculations we found that the mRS has not decreased as in our first calculations. The corrected data are now inserted in the manuscript in table 2 and we have changed the result section at page 9, line 7: (50 % versus 87.5 ..). Actually there were 7 patients with missing data according to mRS after 3 months cases that had been misclassified to having a high mRS instead of missing data. We apologize for this erratum. However, we have added a sentence to mitigate our assumption in the conclusion (page 13, line 5): ... that the risk for IVT-associated complications in this group is low.

### Comment 4

We should be cautious when suggesting that patients under 40 years have higher odds to be a stroke mimics, as although the proportion of those patients in the stroke group is small (2%), the absolute number is similar to that of the mimics group (11 vs. 12).

Reply: We agree with the reviewer that this statement is too strong and have therefore weakened our statement due to the low numbers under study. We have therefore rephrased and also added OR in the Abstract, Results, line 13-14: Age of less than 40 years may be a predictor for a patient to be a stroke mimic (OR 8.7 (3.2-24.0),  $p < 0,0001$ ).

### Comment 5

A total of 699 patients were recruited in the thrombolysis registry but only 674 were included in final analysis. Please, clarify the reason of excluding 25 patients.

Reply: We excluded patients that had previously been treated with IVT. Hence, 25 patients were excluded due to previous treatment with rTPA. We have now clarified this at page 7, line 16:.... 25 patients were excluded due to previous treatment with IVT.

### Comment 6

Please, clarify what do you mean with “Symptom-diagnoses” and “observational diagnosis”

Reply: We apologize for not being clear in defining the final “true” diagnoses in the stroke mimicking group. “Symptom diagnoses” and observational diagnoses indicate descriptive diagnoses without any defined etiology. We have therefore merged symptom diagnoses and observational diagnosis into one variable: symptom diagnoses, and clarified this variable. On page 8, line 13-15, we have added: , 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,

### Comment 7 and 8

In table 1 it is reported that up to 25% of stroke mimics had a previous stroke or TIA. Do they really were prior stroke/TIA or could they be also stroke mimics?

Reply: Thanks for the remark. We have retrospectively scrutinized all the medical records for all stroke mimics and have assured that 12 of the 48 stroke mimics had been hit by a previous stroke. Moreover we validated the stroke mimics by assessing the medical journals 3 months after the

ischemic stroke. One cannot be completely sure of the previous stroke/TIA, but medical journal were re-evaluated, and electronic journals are available from 2002 in our electronic medical records. In addition, 15 patients received IVT on more than one occasion. Do any stroke mimic receive IVT more than once?

Reply: No patient received IVT more than once in this cohort.

Reviewer: 2

Reviewer Name: Georgios Tsivgoulis

Institution and Country: National and Kapodistrian University of Athens

Comment 1

Abstract: "(72 versus 52 years". The authors should also provide the corresponding standard deviations.

Reply: We have now inserted interquartile ranges (IR). We prefer IR, as this variable is not normally distributed. Changes have been made at page 2, line 13-14: (interquartile range: 64-81) versus 54 years (interquartile range 40-67)

Comment 2

Abstract: "(OR 10,3,  $p < 0,0001$ ". The authors should also provide the corresponding confidence intervals

Reply: Thanks for the remark. The corresponding CIs and the correct OR have now been inserted.

Comment 3

Abstract: "Stroke mimics receiving IVT had a favorable outcome" could be better rephrased to "Stroke mimics receiving IVT had a more favorable outcome"

Reply: Thank you for this suggestion, we have rephrased in the Abstract, Conclusions, line 21: Stroke mimics receiving IVT had a more favorable outcome compared to stroke patients,..

Comment 4

Introduction: "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". It is not only a matter of limited availability, brain MRI may be time-consuming and thus delay prompt IVT treatment.

Reply: We agree with the reviewer that this needed to be clarified and have therefore added at page 4, line 18-20: However, this is not only limited by the availability of MRI scans in acute stroke, but also the time it takes to assess an patient with an MRI scan.

Comment 5

Introduction: The authors should also cite a very recent meta-analysis on the safety of intravenous thrombolysis in stroke mimics (Stroke. 2015;46:1281-7)

Reply: Thank you for suggesting this important meta-analysis, which is now mentioned in the Introduction part. On page 4, line 11-14 we have added: 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

Comment 6

- "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." It should be clearly stated by the authors who is responsible for IVT administration in their institution: the internist, the neurologist or the emergency doctor? If the neurologist is available only during office hours, who is in charge for AIS patients eligible for IVT presenting out of office hours?

Reply: We apologize for not having properly clarified the process of decision making according to allocation to rTPA treatment. At Södersjukhuset all IVT treatment decisions during office hours are made by a neurologist. During non-office hours the decisions are supported by a neurologist on call. This is now clarified at page 5, line 5-8 we have added: 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 IVT cases.

Comment 7

- "dator-tomographic imaging". Do authors mean "computed-tomography imaging"?

Reply: Yes, we are meaning computed-tomography imaging. We have now changed this at page 6, line 12.

Comment 8

- Some of the final diagnoses reported by the authors (eg. Bell's palsy) are not difficult to differentiate from an acute ischemic stroke by an experienced neurologist. Some other final diagnoses are vague (eg. headache, symptom-diagnoses, observational diagnoses). The authors should further elucidate the aforementioned stroke mimic categories.

Reply: We agree that some of the diagnoses are easy to differentiate, such as Bell's palsy. Nevertheless, two patients with Bell's palsy were assessed as stroke mimics, which may reflect the risk of misdiagnosis when evaluating patients during time pressure. However, we are aware of being somewhat vague in the first definition of the final diagnoses. We have now clarified these diagnoses and further merged "symptom diagnoses" and "observational diagnoses" into one variable. Please see our reply to reviewer 1,

Comment 9.

- "The work-up of the patients not undergoing an MRI increases the chance of missing out on stroke mimics". This is not entirely true. MRI could also reveal true stroke cases considered and incorrectly classified as mimics.

Reply: This is an important remark, and we have therefore clarified our sentence and added at page 11, line 6-7: ...,further radiological work-up with MRI could arguably exclude a stroke mimic, but also indicate a stroke when considered a mimic.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Georgios Tsivgoulis National and Kapodistrian University of Athens, Greece
<b>REVIEW RETURNED</b>	14-Jun-2017

<b>GENERAL COMMENTS</b>	The authors responded successfully to all comments.
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