Safety of Intravenous Thrombolysis in Stroke Mimics
Prospective 5-Year Study and Comprehensive Meta-Analysis

Georgios Tsivgoulis, MD; Ramin Zand, MD; Aristeidis H. Katsanos, MD; Nitin Goyal, MD; Ken Uchino, MD; Jason Chang, MD; Efthimios Dardiotis, MD; Jukka Putaala, MD; Anne W. Alexandrov, PhD; Marc D. Malkoff, MD; Andrei V. Alexandrov, MD

Background and Purpose—Shortening door-to-needle time may lead to inadvertent intravenous thrombolysis (IVT) administration in stroke mimics (SMs). We sought to determine the safety of IVT in SMs using prospective, single-center data and by conducting a comprehensive meta-analysis of reported case-series.

Methods—We prospectively analyzed consecutive IVT-treated patients during a 5-year period at a tertiary care stroke center. A systematic review and meta-analysis of case-series reporting safety of IVT in SMs and confirmed acute ischemic stroke were conducted. Symptomatic intracerebral hemorrhage was defined as imaging evidence of ICH with an National Institutes of Health Stroke Scale increase of ≥24 points. Favorable functional outcome at hospital discharge was defined as a modified Rankin Scale score of 0 to 1.

Results—Of 516 consecutive IVT patients at our tertiary care center (50% men; mean age, 60±14 years; median National Institutes of Health Stroke Scale, 11; range, 3–22), SMs comprised 75 cases. Symptomatic intracerebral hemorrhage occurred in 1 patient, whereas we documented no cases of orolingual edema or major extracranial hemorrhagic complications. In meta-analysis of 9 studies (8942 IVT-treated patients), the pooled rates of symptomatic intracerebral hemorrhage and orolingual edema among 392 patients with SM treated with IVT were 0.5% (95% confidence interval, 0%–2%) and 0.3% (95% confidence interval, 0%–2%), respectively. Patients with SM were found to have a significantly lower risk for symptomatic intracerebral hemorrhage compared with patients with acute ischemic stroke (risk ratio=0.33; 95% confidence interval, 0.14–0.77; P=0.010), with no evidence of heterogeneity or publication bias. Favorable functional outcome was almost 3-fold higher in patients with SM in comparison with patients with acute ischemic stroke (risk ratio=2.78; 95% confidence interval, 2.07–3.73; P<0.00001).

Conclusions—Our prospective, single-center experience coupled with the findings of the comprehensive meta-analysis underscores the safety of IVT in SM. (Stoke. 2015;46:1281-1287. DOI: 10.1161/STROKEAHA.115.009012.)

Key Words: intracranial hemorrhages ▪ misdiagnosis ▪ safety ▪ stroke ▪ tissue-type plasminogen activator

Numerous patients may present in the emergency department with different nonvascular neurological conditions that closely resemble stroke, which are referred to as stroke mimics (SMs). The incidence of SMs in patients with initially suspected stroke varies widely across studies (4.8%–31%), with the largest study to date reporting that nearly one third of the acute neurological deficits are not attributable to cerebrovascular disease.2

The benefit of intravenous thrombolysis (IVT) in patients with acute ischemic stroke (AIS) is time-dependent and decreases as time from stroke onset to treatment initiation increases. Consequently, current American Heart Association recommendations advocate shortening door-to-needle time to increase the delivery of tissue-type plasminogen activator (tPA) among patients with AIS.3 Moreover, the proportion of patients with AIS eligible for IVT who receive it within the appropriate time window, as well as the percentage of patients with AIS treated with tPA with a door-to-needle time of ≤60 minutes, have been established as core metrics for measuring the quality of care at stroke centers.4

However, the efforts to increase the availability of tPA and shorten door-to-needle time may lead to inadvertent IVT administration in patients with SMs. A common concern among emergency physicians for precluding tPA use...
is the argument indicating that the treatment benefit from IVT may be counterbalanced by the potential for harm to patients presenting with conditions mimicking AIS.5-9 The available data about the outcomes of patients with SMs inadvertently treated with AIS are almost exclusively limited in single-center case-series studies including small numbers of patients (≤100).10-22

In view of the former considerations, the aim of this study was to determine the safety of IVT in SMs by presenting prospective, single-center data from a tertiary care stroke center for a 5-year period and by conducting a comprehensive meta-analysis of all available case series.

Methods

Single-Center Study Population and Methods

Consecutive patients treated with IVT from a tertiary care stroke center (Memphis, TN) were prospectively identified and analyzed during a 5-year period (2009–2013). Noncontrast head computed tomography, National Institutes of Health Stroke scale (NIHSS) pretreatment, and modified Rankin Scale scores at discharge were obtained as standard of care. Pretreatment systolic and diastolic blood pressure levels were measured using automated cuffs. Ischemic lesions on brain magnetic resonance imaging studies that were routinely performed as part of diagnostic work-up (within 48 hours from symptom onset) were read by radiologists unaware of the purposes of this study. All magnetic resonance imaging studies included a diffusion-weighted imaging sequence and the presence of ischemia. Further details about institutional review board–approved stroke registry at our institution have been previously described.14

Initial stroke diagnosis in the emergency department was compared with the final hospital discharge diagnosis. Stroke diagno- ses other than AIS were recorded. The conclusion that the presenting symptoms represented SM was based on the absence of ischemic lesions on diffusion-weighted imaging sequences and the presence of an alternate clinical discharge diagnosis as previously described by others.31-33 Symptomatic intracerebral hemorrhage (sICH) was defined as imaging evidence of ICH with an NIHSS increase of ≥4 points.15,20 Major and minor extracranial hemorrhagic complications after systemic thrombolysis were documented using GUSTO (Global Use of Strategies to Open Occluded Arteries) bleeding criteria.34 Favorable functional outcome (FFO) at hospital discharge was defined as a modified Rankin Scale score of 0 or 1.20

Search Strategy and Data Extraction From Previous Studies

The meta-analysis adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses.24 Eligible observational studies reporting the use of IVT in SMs were identified by searching MEDLINE and SCOPUS. The following combination of search strings was used in both database searches: SMs, stroke misdiagnosis, thrombolysis, and tPA. No language or other restrictions were imposed. Last literature search was conducted on September 13, 2014.

Reference lists of all articles that met the inclusion criteria and of relevant review articles were examined to identify studies that may have been missed by the database search. All retrieved studies and reference lists were scanned independently by 2 reviewers (G.T. and A.H.K.). In the final presentation of the literature search results, there were no discrepancies between the 2 authors. Both prospective and retrospective study protocols were included in the present analysis. No certain sample size was used as an exclusion criterion for a study and no language or other restrictions were imposed. Last literature search was conducted on September 13, 2014.

In each study that met the inclusion criteria, a predefined 10-point quality control was used to address for biases.25 For each quality item, the corresponding risk of bias was categorized as low, high, or unclear according to the suggestions by Higgins et al.26 Unavailable data were categorized by convention as unclear risk of bias. Quality control and bias identification were performed by 3 independent reviewers (G.T., R.Z., and A.H.K.), and all emerging conflicts were resolved with consensus.

Data on safety of IVT in both patients with SMs and AIS were extracted independently by the 2 authors, who performed the literature search (G.T. and A.H.K.). We contacted authors of selected studies and asked to provide additional data when not available in the relevant publication. The present analyses including additional information by the authors of 2 studies are available in the online-only Data Supplement.11,21 Safety was assessed by comparing the pooled sICH and orolingual edema (OE) rates in patients with SMs and confirmed AIS treated with intravenous tPA. Finally, we performed consecutive subgroup analyses for all available baseline characteristics between the SM and AIS subgroups.

Statistical Analyses

Single-Center Study Data

Continuous variables are presented as means±SD (normal distribution) and as median with interquartile range (skewed distribution). Categorical variables are presented as percentages with corresponding 95% confidence intervals (CIs). The adjusted Wald method, which provides the best coverage for binomial CI when samples are ≈150,27 was used for computation of 95% CI of sICH and OE prevalence among patients with SMs. Statistical comparisons were performed between patients with SMs and confirmed AIS using the χ² test, Fisher exact test, unpaired t test, and Mann–Whitney U-test as indicated for dichotomous or continuous variables. The statistical package for Social Science (SPSS Inc, version 13.0 for Windows) was used for statistical analyses of single-center study data.

Meta-Analysis

For each study, the numbers of events in patients with SM and AIS were identified and a risk ratio (RR) was calculated. For studies with a zero cell, we used a continuity correction of 0.5, as appropriate. In cases of ≥2 zero cells, the assumption of continuity correction was not used and the corresponding point estimates were designated as not estimable.28 The overall RR for all pooled studies was computed using the random effects method (DerSimonian and Laird). Heterogeneity between studies was assessed by the Cochran Q and P statistic as previously described.29 Heterogeneity was considered as statistically significant when the P value derived from Cochran Q was <0.1. For the qualitative interpretation of heterogeneity, P values of at least 50% are usually considered to represent substantial heterogeneity, whereas values of at least 75% indicate considerable heterogeneity according to the Cochrane Handbook.30 In subgroup analyses, we used the mixed-effects model to calculate both the pooled point estimate in each subgroup and the overall estimate. According to the mixed-effects model, we used a random effects model (DerSimonian and Laird) to combine studies within each subgroup and a fixed effect model (Mantel–Haenszel method) to combine subgroups and estimate the overall effect. We assumed the study-to-study variance (τ-squared) to be the same for all subgroups, τ-squared was first computed within subgroups and then pooled across subgroups. A χ² test for heterogeneity was performed across subgroup results, and the corresponding P value was considered statistically significant if it is <0.05. Publication bias was assessed at the overall analysis graphically using a funnel plot and with Egger test for funnel plot asymmetry.31

Statistical analyses were conducted using Review Manager (RevMan) Version 5.3 software (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and Comprehensive Meta-analysis Version 2 software (M. Borenstein, L. Hedges, J. Higgins, H. Rothstein; Biostat, Englewood, NJ, 2005).
Results

Single-Center Study Data

Of 516 consecutive IVT patients at our tertiary care center during the study period, SMs comprised 75 cases (14.5%; 95% CI by adjusted Wald method, 11.7%–17.9%). Baseline characteristics and outcomes in patients with SMs and AIS are presented in Table 1. Conversion disorder (23%) followed by seizures (20%) and complicated migraine (20%) was the most common final diagnoses in patients with SMs treated with tPA. Hypertension was the most prevalent risk factor (44%) followed by diabetes mellitus (28%). History of psychiatric disorder was documented in 12% of SM cases. Mean pretreatment systolic and diastolic blood pressures were 164±29 and 91±18 mm Hg, respectively. sICH occurred in 1 patient (1.3%; 95% CI by adjusted Wald method, 0%–7.9%) who experienced a substantial neurological deterioration within 12 hours after tPA infusion (Figure I in the online-only Data Supplement). This patient with a history of hypertension and alcoholism presented acutely with dysarthria and mild right hemiparesis (NIHSS score, 6 points). Metabolic encephalopathy was the final diagnosis of his acute neurological presentation, whereas uncontrolled hypertension may have accounted for the tPA-related sICH. The patient died during the third day of hospitalization. We documented no cases of OE (0%; 95% CI by adjusted Wald method, 0%–4.2%) or major extracranial hemorrhagic complications (0%; 95% CI by adjusted Wald method, 0%–4.2%). Two patients experienced minor extracranial hemorrhagic complications (1 case of gingival and 1 case of nose bleeding) requiring no blood transfusion. The median length of hospitalization patients with SMs was 3 days (interquartile range, 2–4 days), whereas FFO at hospital discharge was achieved in 88% of cases (95% CI by adjusted Wald method, 79%–94%).

Meta-Analysis of Case Series

MEDLINE and SCOPUS database search yielded 47 and 79 results, respectively. After removing duplicates, the titles and abstracts from the remaining 96 studies were screened and 13 potentially eligible studies for the meta-analysis were retained. After retrieving the full-text version of the aforementioned 13 studies, 5 studies were excluded because they reported data that were already published in previous studies (overlapping data).11-14 In the final presentation of the literature search results, there was no conflict or disagreement between the 2 reviewers and the 8 studies that met the study protocol’s inclusion criteria15-22 together with the data from the protocol of this study were included both in the qualitative and quantitative synthesis (Figure 1). The characteristics and bias assessment of the included studies, comprising 8942 total patients with IVT and 392 patients with SMs (4.38%), are shown in Table I in the online-only Data Supplement. Figure II in the online-only Data Supplement summarizes the risk of bias in individual case-series studies included in this meta-analysis. The risk of bias was high in terms of binding of outcome assessment (because the final SM and sICH diagnoses were made by the same treating physicians in the majority of

Table 1. Baseline Characteristics and Outcome Variables in Patients With Stroke Mimics and Confirmed AIS Treated With Intravenous Thrombolysis During a 5-Year Period in a Tertiary Care Stroke Center (Memphis, TN)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke Mimics (n=75)</th>
<th>Confirmed AIS (n=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y, SD</td>
<td>56±12</td>
<td>60±14</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>32 (43%)</td>
<td>226 (51%)</td>
</tr>
<tr>
<td>Median baseline NIHSS, points (IQR)</td>
<td>6 (3–9)</td>
<td>11 (3–22)</td>
</tr>
<tr>
<td>Mean door-to-needle time, min (SD)</td>
<td>66 (32)</td>
<td>63 (24)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>33 (44%)</td>
<td>368 (83%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>21 (28%)</td>
<td>185 (42%)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>19 (25%)</td>
<td>251 (57%)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>20 (27%)</td>
<td>160 (36%)</td>
</tr>
<tr>
<td>Mean pretreatment SBP, mm Hg (SD)</td>
<td>142 (24)</td>
<td>164 (29)</td>
</tr>
<tr>
<td>Mean pretreatment DBP, mm Hg (SD)</td>
<td>83 (11)</td>
<td>91 (18)</td>
</tr>
<tr>
<td>Mean pretreatment blood glucose, mg/dL (SD)</td>
<td>128 (32)</td>
<td>141 (58)</td>
</tr>
<tr>
<td>Symptomatic intracranial hemorrhage, n (%)</td>
<td>1 (1.3%; 95% CI,* 0%–7.9%)</td>
<td>5 (1.13%; 95% CI,* 0%–2.7%)</td>
</tr>
<tr>
<td>Orolingual edema, n (%)</td>
<td>0 (0%; 95% CI,* 0%–4.2%)</td>
<td>0 (0%; 95% CI,* 0%–0.7%)</td>
</tr>
<tr>
<td>Major extracranial hemorrhagic complications, n (%)</td>
<td>0 (0%; 95% CI,* 0%–4.2%)</td>
<td>0 (0%; 95% CI,* 0%–0.7%)</td>
</tr>
<tr>
<td>Minor extracranial hemorrhagic complications, n (%)</td>
<td>2† (2.7%; 95% CI,* 0%–9.8%)</td>
<td>NA</td>
</tr>
<tr>
<td>Median length of hospitalization, d (IQR)</td>
<td>3 (2–4)</td>
<td>6 (1–11)</td>
</tr>
<tr>
<td>Functional independence at hospital discharge, n (%)‡</td>
<td>66 (88%; 95% CI,* 79%–94%)</td>
<td>172 (39%; 95% CI,* 34.5%–43.6%)</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>1 (1.3%; 95% CI,* 0%–7.9%)</td>
<td>38 (8.6%; 95% CI,* 6.3%–11.6%)</td>
</tr>
</tbody>
</table>

AIS indicates acute ischemic stroke; CI, confidence interval; DBP, diastolic blood pressure; IQR, interquartile range; NIHSS, National Institutes of Health Stroke scale; and SBP, systolic blood pressure.

*Calculated by the adjusted Wald method.
†One case of gingival and 1 case of nose bleeding.
‡Defined as a modified Rankin Scale score of 0–1 at discharge.
studies) and in terms of prospective data collection (given the retrospective design in the majority of studies).

All analyses presented in the meta-analysis include data from the 8 published studies and our unpublished single-center data. The pooled rates of sICH and OE among 392 patients with SMs treated with IVT were 0.5% (95% CI by adjusted Wald method, 0%–2%; n=2) and 0.3% (95% CI by adjusted Wald method, 0% to 2%; n=1), respectively (Table 2). In the overall analysis of 9 case-series studies (with available information in the prevalence of sICH in 392 patients with SMs and 8042 patients with confirmed AIS), patients with SMs were found to have a significantly lower risk for sICH after thrombolysis compared with patients with confirmed AIS (RR=0.33; 95% CI, 0.14–0.77; P=0.010; Figure 2A), with no evidence of heterogeneity (I²=0%; P=0.93; Figure 2A) or publication bias (P=0.151; Egger test; Figure III in the online-only Data Supplement). In view of the limited number of sICH cases (n=2), we repeated our analyses after excluding studies reporting no sICH complications in SMs (in which a continuity correction of 0.5 was originally used as appropriate). The previous findings reproduced that a lower risk for sICH was observed in patients with SMs treated with IVT in comparison with confirmed AIS patients receiving intravenous tPA (RR=0.21; 95% CI, 0.05–0.83; P=0.030; Figure 2B), with no evidence of heterogeneity (I²=0%; P=0.85; Figure 2B). The risk of OE after systemic thrombolysis was not found to be significantly different between patients with SMs and AIS (RR=1.15; 95% CI, 0.35–3.72), with no evidence of heterogeneity within studies (I²=0%; P=0.54).

The pooled rate of FFO at hospital discharge was 84.5% (95% CI, 63.8%–94.4%; Table 2). In the overall analysis of 4 case-series studies (with available information in the prevalence of FFO at discharge or at 3 months in 296 patients with SMs and 6732 patients with confirmed AIS), the RR of FFO

Table 2. Pooled Rates of Outcomes With Corresponding 95% CI of Patients With SM Treated With Intravenous Thrombolysis Across Different Case-Series Studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n (Studies)</th>
<th>n (SM)</th>
<th>Pooled Rates (95% CI)</th>
<th>P</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic intracranial hemorrhage</td>
<td>9</td>
<td>392</td>
<td>0.5% (0%–2%)</td>
<td>0%</td>
<td>0.941</td>
</tr>
<tr>
<td>Orolingual edema</td>
<td>7</td>
<td>315</td>
<td>0.3% (0%–2%)</td>
<td>0%</td>
<td>0.913</td>
</tr>
<tr>
<td>Favorable functional outcome†</td>
<td>4</td>
<td>206</td>
<td>84.5% (63.8%–94.4%)</td>
<td>78.7%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and SM, stroke mimics.
*Cochran Q statistic.
†Defined as a modified Rankin Scale score of 0–1 at discharge.
at discharge was almost 3-fold higher in patients with SMs (RR = 2.78; 95% CI, 2.07–3.73; P < 0.0001; Figure 3) in comparison with patients with confirmed AIS, with substantial evidence of heterogeneity across studies that reported data at discharge (I² = 82%; P = 0.003; Figure 3).

Table II in the online-only Data Supplement presents the comparative analyses of baseline characteristics in patients with SMs and confirmed AIS treated in different case series. Female sex and younger age were more common in SMs, whereas hypertension and atrial fibrillation were more prevalent in patients with confirmed AIS. Finally, patients with confirmed AIS presented with higher systolic blood pressure levels at the emergency department in comparison with patients with SMs. The median NIHSS scores with their corresponding interquartile ranges in patients with SMs and confirmed AIS across different case series are presented in Figure IV in the online-only Data Supplement. Patients with SMs had lower admission NIHSS scores in the majority of reported series.

**Discussion**

Our prospectively collected single-center data, coupled with the findings of the comprehensive meta-analysis, underscore the safety of IVT in SMs given the lower risk of symptomatic intracranial hemorrhagic complications compared with IVT-treated patients with subsequently confirmed AIS. Moreover,
the pooled rates of sICH and OE in patients with SMs treated with systemic thrombolysis are extremely low (≤0.5%) with narrow 95% CI (not exceeding 2%), whereas almost 9 of 10 patients with SMs treated with intravenous tPA have a FFO at hospital discharge.

The present data indicate that IVT does not adversely affect the favorable natural history of SMs, and treatment benefit from tPA would not be counterbalanced by the potential for harm to patients presenting with conditions mimicking AIS, an argument based on scarce data from case reports that has been frequently used by emergency physicians unwilling to treat patients with tPA. Moreover, the lack of any heterogeneity in terms of the prevalence of thrombolysis-related complications across different registries reporting outcomes in patients with SMs treated with IVT should be noted. This observation further underlines the safety of tPA administration in patients presenting with conditions mimicking AIS at stroke centers with expertise in systemic thrombolysis. Although these data should not be relied on as an excuse for not carefully evaluating for alternative diagnoses in patients presenting with acute focal neurological dysfunction in the emergency department, our findings do provide a measure of reassurance to stroke and emergency physicians that, even if their clinical judgment is incorrect, treatment with tPA is unlikely to be complicated if administered in keeping with the established criteria.

The findings of the present meta-analysis about differences in baseline characteristics between patients with SMs and AIS corroborate the observations of prospective cohort studies, whose aim was the development of a recognition instrument for SMs in the emergency department. In the Telestroke Mimic Score advanced age, positive medical history for hypertension, atrial fibrillation, and antiplatelet/anticogulant therapy, together with high NIHSS, facial/limb weakness, and speech problem on admission, were regarded as negative predictors for the diagnosis of SMs. In the Brain Attack Study, SM diagnosis was associated with cognitive impairment and abnormal signs in other systems, whereas confirmed AIS was related to vascular risk factors, abnormal vascular findings, and focal neurological signs that enable lesion localization in 1 cerebral hemisphere or a clinical stroke syndrome determination.

In the interpretation of this report, certain limitations need to be acknowledged. The difference observed in the percentage of patients with SMs treated with tPA between our single-center study cohort (14.5%) and the percentage derived from the coupled meta-analysis of all case-series (4.4%) could be attributed to the prospective design of our study capturing a larger number of SMs and to the more aggressive approach in our center about the administration of systemic thrombolysis in patients presenting with potential symptoms of acute cerebral ischemia. Apart from our tertiary care center study, patient data were prospectively collected only in the study by Förster et al. Moreover, selection bias cannot be ruled out in the present meta-analysis as the consecutiveness of the study participants was clearly stated in 5 of 9 included studies, including the present study protocol. Excluding patients after initial recruitment was mentioned in 4 studies. Reporting bias is also probable, as blinding in outcome assessment was not reported in any of the previous study protocols.

Moreover, in 2 studies, ≥21 authors reported research support from pharmaceutical companies that manufacture tPA and this may constitute an additional source of bias. Finally, other complications of IVT, including asymptomatic intracranial hemorrhages, were not recorded in the majority of case-series studies and the prevalence of these complications among patients with SMs cannot be determined in the present meta-analysis.

In conclusion, our single-center experience in combination with the findings of our meta-analysis underscores the safety of systemic thrombolysis in SMs given the low prevalence of hemorrhagic and systemic complications and the lack of heterogeneity across reported case series. They also provide reassurance to stroke physicians that the possibility that patients with stroke symptoms may represent SMs should not preclude the administration of tPA on the basis of safety concerns.

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Disclosures
Dr. Alexandrov declares speaking engagements with Genentech, Inc. Dr. Alexandrov discloses advisory relationship with Genentech, Inc. The other authors report no conflicts.

References


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**Supplemental Table I. Characteristics of the case-series included in meta-analysis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Center</th>
<th>Study period</th>
<th>N of patients treated with IVT</th>
<th>Stroke mimics (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chernyshev et al¹</td>
<td>2010</td>
<td>Houston</td>
<td>2004-2008</td>
<td>512</td>
<td>69 (13.5%)</td>
</tr>
<tr>
<td>Forster et al²</td>
<td>2012</td>
<td>Mannheim</td>
<td>2004-2010</td>
<td>648</td>
<td>42 (6.5%)</td>
</tr>
<tr>
<td>Guillan et al³</td>
<td>2012</td>
<td>Madrid</td>
<td>2004-2011</td>
<td>621</td>
<td>15 (2.4%)</td>
</tr>
<tr>
<td>Mehta et al⁴</td>
<td>2014</td>
<td>St. Louis</td>
<td>2011-2012</td>
<td>120</td>
<td>20 (16.7%)</td>
</tr>
<tr>
<td>Scott et al⁵</td>
<td>2003</td>
<td>Michigan</td>
<td>1996-2001</td>
<td>151</td>
<td>6 (4.0%)</td>
</tr>
<tr>
<td>Tsivgoulis et al⁶</td>
<td>2011</td>
<td>Phoenix</td>
<td>2003-2008</td>
<td>539</td>
<td>56 (10.4%)</td>
</tr>
<tr>
<td>Tsivgoulis et al</td>
<td>-</td>
<td>Memphis</td>
<td>2009-2013</td>
<td>516</td>
<td>75 (14.5%)</td>
</tr>
<tr>
<td>Uchino et al⁷</td>
<td>2010</td>
<td>Pittsburgh</td>
<td>2002-2005</td>
<td>254</td>
<td>9 (3.5%)</td>
</tr>
<tr>
<td>Zinkstok et al⁸</td>
<td>2013</td>
<td>Multicenter</td>
<td>Varies among centers</td>
<td>5581</td>
<td>100 (1.8%)</td>
</tr>
</tbody>
</table>

IVT: intravenous thrombolysis, N: number
Supplemental Table II. Subgroup analyses of baseline characteristics between stroke mimics and confirmed acute ischemic stroke patients treated with intravenous thrombolysis across different case-series studies.

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>N*</th>
<th>Stroke Mimics</th>
<th>Acute Ischemic Stroke</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7</td>
<td>56.5 (53.3 – 59.7)</td>
<td>67.7 (65.1 – 70.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Males (%)</td>
<td>7</td>
<td>44.2 (38.8 - 49.6)</td>
<td>54.7 (52.6 - 56.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>8</td>
<td>44.7 (33.7 - 56.1)</td>
<td>63.9 (54.3 - 72.4)</td>
<td>0.012</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>7</td>
<td>40.1 (30.1 – 51.1)</td>
<td>42.7 (33.9 - 52.0)</td>
<td>0.720</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8</td>
<td>17.8 (13.3 - 23.4)</td>
<td>22.7 (19.9 – 25.8)</td>
<td>0.120</td>
</tr>
<tr>
<td>Atrial Fibrillation (%)</td>
<td>8</td>
<td>7.2 (4.5 - 11.2)</td>
<td>22.8 (19.1 - 27.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>5</td>
<td>13.3 (8.3 - 20.8)</td>
<td>18.5 (14.0 – 23.9)</td>
<td>0.228</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>7</td>
<td>27.2 (20.0 - 35.8)</td>
<td>23.7 (19.4 - 30.9)</td>
<td>0.618</td>
</tr>
<tr>
<td>Admission SBP (mmHg)</td>
<td>3</td>
<td>143.2 (137.4 – 149.1)</td>
<td>157.8 (152.7 – 163.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Admission DBP (mmHg)</td>
<td>3</td>
<td>103.1 (51.6 – 154.5)</td>
<td>109.2 (57.8 – 160.6)</td>
<td>0.869</td>
</tr>
</tbody>
</table>

*N indicates the number of case-series studies that provided data for the analysis

SBP: systolic blood pressure; DBP: diastolic blood pressure

Continuous variables are presented as mean (95%CI); non-continuous variables are presented as % (95%CI)
Supplemental Figures and Figure Legends

Supplemental Figure I. Symptomatic intracranial hemorrhage complicating a stroke mimic patient treated with intravenous thrombolysis. Pre-treatment CT-scan excludes the presence of intracranial hemorrhage (A). Post-treatment CT-scan performed at three hours following tPA-bolus (due to clinical deterioration of the patient coupled with worsening of the level of consciousness) shows massive left thalamic hemorrhage with intra-ventricular extension causing hydrocephalus (B).
Supplemental Figure II. Risk of bias in the individual studies that were included for meta-analysis (low risk= bias, if present, is unlikely to alter the results seriously, unclear risk= a risk of bias that raises some doubt about the results, high risk= bias may alter the results seriously).
Supplemental Figure III. Funnel plot assessing the risk of publication bias across the included case series.
Supplemental Figure IV. Median NIHSS-score with their corresponding interquartile ranges in stroke mimics (SM) and confirmed acute ischemic stroke patients (AIS) across different case series.
Supplemental References


