Optimizing thrombolysis in acute ischaemic stroke
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CHAPTER 6

SAFETY OF THROMBOLYSIS IN STROKE MIMICS: RESULTS FROM A MULTICENTER COHORT STUDY

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ABSTRACT

Background
Intravenous thrombolysis (IVT) for acute ischaemic stroke is beneficial within 4.5 hours of symptom onset, but the effect rapidly decreases over time necessitating quick diagnostic work-up. Initial time strain occasionally results in treatment of patients with an alternate diagnosis (‘stroke mimics’). We investigated whether IVT is safe in these patients.

Methods
In this multicenter observational cohort study containing 5518 consecutive patients treated with IVT, we determined the frequency and the clinical characteristics of stroke mimics. For safety, we compared the rate of symptomatic intracranial haemorrhage (SICH, ECASS-II definition) in patients with stroke mimics to patients with ischaemic strokes.

Results
One hundred patients with stroke mimics (1.8%, 95% CI 1.5–2.2) were identified. Patients with stroke mimics were younger, more often women, had less risk factors except smoking and previous stroke or transient ischaemic attack. The SICH rate in stroke mimics was 1.0% (95% CI 0.0–5.0) compared to 5.5% (95% CI 4.9–6.1) in ischaemic strokes.

Conclusion
In experienced stroke centres, among patients treated with IVT only few had a final diagnosis other than stroke. Complication rate in these stroke mimics was low.
INTRODUCTION

Intravenous thrombolysis (IVT) is the only approved therapy in patients with acute ischaemic stroke presenting within 4.5 hours after symptom onset.¹,² Unfortunately, the benefit of IVT rapidly declines over time from symptom onset.³ Aiming at a prompt start of IVT after hospital arrival, time for initial diagnostic work-up is limited. Occasionally, this results in treatment of patients who finally turn out to have an alternate diagnosis, so called ‘stroke mimics’. However, IVT is not without risks since symptomatic intracranial haemorrhage (SICH) is reported in 2–9% after IVT in stroke patients.¹,²,⁴,⁵

The proportion of stroke mimics varies between 1 and 16% in hospital-based IVT registers.⁶-¹⁵ Knowledge of safety of IVT in stroke mimics is important since treatment in these patients can only be accepted as long as the complication rate is very low. Serious complications of IVT in stroke mimics have not been reported so far, but most studies were single centre and based on a relatively small number of patients.⁶-¹⁵ The aim of the current study is to investigate the frequency and clinical characteristics of stroke mimics from a large cohort of patients treated with IVT, and to assess the safety of IVT treatment in stroke mimics.

METHODS

Study population

In a collaboration of 12 European stroke centres, we designed a large cohort of IVT treated ischaemic stroke patients to study outcomes of IVT, reflecting routine clinical practice.¹⁶,¹⁷ Each centre reported on the period for which they had prospectively collected data on consecutive patients treated with IVT up to December 31, 2011. Treatment with IVT is performed according to current guidelines in all centers by administering 0.9 mg/kg alteplase (maximum 90 mg) within 4.5 hours of symptom onset.¹⁸,¹⁹
Data collection
Complete individual patient data were collected with a standardized form with predefined variables as it was used in previous studies.\textsuperscript{16,27} Local investigators filled in the forms systematically using prospectively ascertained in-hospital thrombolysis and stroke registers. Completed forms from all centres were compiled in the coordinating Academic Medical Center, where the analyses of the pooled data were performed.

The following prospectively collected baseline variables were used: age, sex, hypertension, diabetes, atrial fibrillation, hypercholesterolaemia, coronary artery disease, previous ischaemic stroke or transient ischaemic attack, smoking, use of pre-stroke medication, initial stroke severity as assessed by the National Institutes of Health Stroke Scale (NIHSS), blood pressure prior to IVT, serum glucose at admission (mmol/l), and time from symptom onset to IVT. Global aphasia with minimal or no paresis (GAWH) was recorded since it was considered to occur more often in stroke mimics.\textsuperscript{14,20} Presence of GAWH was determined by the NIHSS score indicating global aphasia with $\leq 1$ point for the tested motor items.\textsuperscript{21}

Guiding criteria to distinguish stroke mimics from strokes were derived from Hand et al.,\textsuperscript{22} resembling a previous study on this topic.\textsuperscript{14} Stroke mimics were defined as patients in whom clinical details did not suggest a vascular aetiology but who had an alternate final diagnosis convincingly explaining their symptoms. In case additional diagnostic tests failed to establish an alternate diagnosis but the physician was convinced that, on clinical grounds, the symptoms were not caused by cerebral ischaemia, a stroke mimic was diagnosed as well. On the contrary, stroke was assumed in all patients with history, examination and disease course typical for involvement of an intracerebral vascular territory with supportive or non-contradictory brain imaging. Patients with less convincing clinical features, but no definite conviction of a stroke mimic, were also regarded as stroke. In each center, stroke mimics were retrospectively re-evaluated in detail for complications of IVT and final diagnosis. Patients were diagnosed with migraine when fulfilling the International Headache Society criteria for migraine with aura before or during the follow-up. Diagnosis of a seizure was made on (retrospective) information from a witness suggesting (focal) seizure with a post-
ictal deficit. In case of uncertainty interictal epileptogenic activity on electroencephalography was necessary. Encephalitis was defined as cerebrospinal fluid pleocytosis, with encephalitis convincingly explaining the symptoms. If clinical signs were suggestive for stroke or transient ischaemic attack, ischaemic lesions had to be absent on magnetic resonance imaging (MRI) with diffusion-weighted images (DWI). Four centres participating in this study have published series on this topic before.\(^6,7,14\) Patients reported in these series are included in this study.

**Endpoints**

Primary endpoint was the occurrence of SICH according to the criteria of the European Cooperative Acute Stroke Study II (SICH\(_{\text{ECASS-II}}\): any haemorrhage with neurological deterioration, as indicated by an increase of \(\geq 4\) points on the NIHSS, compared to the value at baseline or the lowest value within 7 days, or any haemorrhage leading to death\(^5\)) since this definition had the largest contribution to worst outcomes in a recent cohort study.\(^23\) We further distinguished SICH according to the criteria of the National Institute of Neurological Disorders and Stroke trial (SICH\(_{\text{NINDS}}\): any haemorrhage plus any neurological deterioration).\(^2\) Fatal ICH was defined as death attributed to ICH, according to the NINDS criteria as well.\(^2\) Other secondary endpoints were mortality, orolingual edema, and functional outcome at 3 months. Functional outcome was assessed by outpatient visits or telephone calls at 3 months using the modified Rankin scale (mRs). Favourable outcome was defined as a mRs score of \(0–2\) and excellent outcome as mRs score of \(0–1\). All endpoints were prospectively collected.

**Standard protocol approvals, registrations, and patients consents**

This study was conducted according to European and national legislations and the medical ethics committee of the Academic Medical Center permitted analysis of the anonymous patient data.

**Statistical analysis**

Baseline characteristics and outcome variables were summarized using descriptive statistics. For categorical variables, we calculated percentage proportions by dividing the number of events by the total number of patients, excluding missing
or unknown cases. Statistics comparing these variables between stroke mimics and strokes included unpaired t, $\chi^2$, Fisher’s exact, and Mann Whitney U tests where appropriate. P-values <0.05 were considered statistically significant. Analyses were done with SPSS version 16.0 (SPSS Inc. Chicago, Illinois, USA).

Literature search
We systematically searched the PUBMED database from Jan 1, 1950 to June 8, 2012 for publications on thrombolysis in stroke mimics, using the following variables (“mimic” OR “misdiagnosis”) AND (“stroke”) AND (“thrombolysis” OR “recombinant tissue plasminogen activator” OR “tissue plasminogen activator” OR “rtPA” OR “tPA” OR “alteplase”). In addition, we searched for relevant studies in the Cochrane Library and Cochrane Central Register of Controlled Trials database from Jan 1, 1993 to June 8, 2012, and hand searched citations from the retrieved studies. Finally, experts in the field were consulted.

RESULTS

Study population and baseline characteristics
In this cohort, 5518 consecutive patients treated with IVT were included. In total, 18.3% (1010 patients) were older than 80 years of age and 9.8% of the patients was treated outside the approved time window (408 patients after 180 minutes before October 2008; 86 patients after 270 minutes from October 2008). In total, 100 patients (1.8%, 95% confidence interval [CI] 1.5-2.2) with a stroke mimic were identified. Demographic and baseline characteristics of the stroke mimics are presented in Table 6.1. Patients with a stroke mimic were younger, more often female, had less risk factors except smoking and previous stroke or transient ischaemic attack. Presentation with GWAH occurred more often in stroke mimics. Stroke mimics were treated at later time points compared to ‘true’ ischaemic strokes. There was a trend towards a higher proportion of stroke mimics that were treated before the end of the time window (i.e. between 165 and 180 minutes before October 2008 and between 255 and 270 minutes from October 2008) than at earlier time points (2.3 versus 1.4%, p=0.09).
### Table 6.1: Clinical characteristics of patients with stroke mimics and ischaemic strokes treated with intravenous thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Stroke mimics (n=100)</th>
<th>Strokes (n=5418)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 (42–76)</td>
<td>70 (60–78)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Women</td>
<td>55 (55.0)</td>
<td>2347 (43.3)</td>
<td>0.020†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (36.1)</td>
<td>3593 (66.4)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (16.5)</td>
<td>1008 (18.7)</td>
<td>0.581†</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (5.2)</td>
<td>1490 (27.8)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>26 (27.1)</td>
<td>1904 (37.9)</td>
<td>0.031†</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>9 (9.3)</td>
<td>873 (17.4)</td>
<td>0.0352†</td>
</tr>
<tr>
<td>Previous ischaemic stroke or TIA</td>
<td>20 (20.6)</td>
<td>650 (13.0)</td>
<td>0.028†</td>
</tr>
<tr>
<td>Current smoking</td>
<td>27 (28.9)</td>
<td>1128 (21.8)</td>
<td>0.134†</td>
</tr>
<tr>
<td>Prior antihypertensives use</td>
<td>17 (24.6)</td>
<td>1951 (55.3)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Prior antiplatelet or anticoagulants use</td>
<td>22 (28.9)</td>
<td>2318 (42.9)</td>
<td>0.014†</td>
</tr>
<tr>
<td>Prior use of statin use</td>
<td>14 (18.7)</td>
<td>1257 (24.8)</td>
<td>0.224†</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>147.3 (24.1)</td>
<td>155.6 (25.4)</td>
<td>0.005‡</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>83.0 (15.0)</td>
<td>84.5 (16.2)</td>
<td>0.421‡</td>
</tr>
<tr>
<td>NIHSS</td>
<td>6 (5–9)</td>
<td>11 (7–17)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>GAWH</td>
<td>17 (20.5)</td>
<td>80 (2.7)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Serum glucose on admission (mmol/l)</td>
<td>6.4 (2.8)</td>
<td>7.2 (2.5)</td>
<td>0.003‡</td>
</tr>
<tr>
<td>Onset to IVT time (minutes)</td>
<td>168 (125–197)</td>
<td>145 (105–180)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Data are number (%), mean (standard deviation), or median (interquartile range).

* Mann Whitney U test; † χ² test; ‡ unpaired t test.

TIA indicates transient ischaemic attack; NIHSS, National Institutes of Health Stroke Scale; GAWH, global aphasia with minor or without hemiparesis; IVT, intravenous thrombolysis.

Eighty-one patients (81%) were diagnosed with either an epileptic seizure (41%), or a psychogenic disorder (28%) or migraine (12%). Other diagnosis were demyelination (5%), encephalitis (3%), brain tumor (2%), peripheral vestibulopathy (2%), posterior reversible constriction syndrome (1%), brachial plexopathy (1%), hypoglycemia (1%), sinusitis (1%), intoxication (1%) and cervical spine haematoma (1%). In two patients (2%), the final diagnosis remained unclear despite extensive work-up, but was definitely non-ischaemic. The period on which centres reported data, the rate of stroke mimics and imaging protocols per centre are presented in Table 6.2.
Table 6.2: Proportion of stroke mimics and imaging protocol per centre

<table>
<thead>
<tr>
<th>Centre</th>
<th>Period (years)</th>
<th>IVT, n</th>
<th>Stroke mimics, n (%)</th>
<th>Treating physician</th>
<th>Routine imaging before IVT</th>
<th>Routine imaging after IVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Municipal Hospital Altenburg, Germany</td>
<td>2004–2008</td>
<td>326</td>
<td>1 (0.3)</td>
<td>S</td>
<td>NCT</td>
<td>NCT or MRI</td>
</tr>
<tr>
<td>Academic Medical Center University of Amsterdam, the Netherlands</td>
<td>2000–2011</td>
<td>447</td>
<td>12 (2.7)</td>
<td>R</td>
<td>NCT</td>
<td>None*</td>
</tr>
<tr>
<td>University Hospital Basel, Switzerland</td>
<td>1998–2011</td>
<td>586</td>
<td>16 (2.7)</td>
<td>S</td>
<td>Until 2009 NCT, CTA</td>
<td>NCT or MRI</td>
</tr>
<tr>
<td>Clinical Center, School of Medicine, University of Belgrade, Serbia</td>
<td>2006–2011</td>
<td>203</td>
<td>5 (2.5)</td>
<td>S</td>
<td>NCT</td>
<td>NCT</td>
</tr>
<tr>
<td>University Hospital Bern, Switzerland</td>
<td>2000–2011</td>
<td>269</td>
<td>0 (0.0)</td>
<td>S</td>
<td>Multimodal MRI or CTA</td>
<td>NCT or CTA</td>
</tr>
<tr>
<td>Brescia University Hospital, Italy</td>
<td>2005–2009</td>
<td>61</td>
<td>4 (6.6)</td>
<td>S or N</td>
<td>NCT</td>
<td>None*</td>
</tr>
<tr>
<td>University Hospital of Heidelberg, Germany</td>
<td>1998–2011</td>
<td>1151</td>
<td>8 (0.7)</td>
<td>S</td>
<td>NCT</td>
<td>NCT</td>
</tr>
<tr>
<td>Helsinki University Central Hospital, Finland</td>
<td>1998–2009</td>
<td>1005</td>
<td>14 (1.4)</td>
<td>S</td>
<td>NCT</td>
<td>NCT</td>
</tr>
<tr>
<td>Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland</td>
<td>2003–2011</td>
<td>396</td>
<td>8 (2.0)</td>
<td>S</td>
<td>NCT, CTA, CTP</td>
<td>NCT, CTA †</td>
</tr>
<tr>
<td>Lille University Hospital, France</td>
<td>2003–2011</td>
<td>430</td>
<td>6 (1.4)</td>
<td>S or N</td>
<td>Until 2009 NCT</td>
<td>Until 2009 NCT</td>
</tr>
<tr>
<td>Nuovo Ospedale Civile, AUSL Modena, Italy</td>
<td>2005–2011</td>
<td>235</td>
<td>4 (1.7)</td>
<td>S or N</td>
<td>From 2009 multimodal MRI</td>
<td>NCT, CTA, CTP</td>
</tr>
<tr>
<td>University Hospital Zurich, Switzerland</td>
<td>2002–2008</td>
<td>409</td>
<td>21 (5.1)</td>
<td>S or N</td>
<td>Contrast-enhanced CT</td>
<td>MRI</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5518</strong></td>
<td><strong>100</strong></td>
<td><strong>100 (1.8)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In absence of complications; †CTA in case of occlusion on initial CTA; ‡NCT in case of contra-indications or rapid deterioration.

CTA indicates computed tomography angiography; CTP, computed tomography perfusion; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; NCT, non-contrast computed tomography; IVT = intravenous thrombolysis, N= general neurologist, R=resident under supervision of neurologist, S=stroke neurologist.
Table 6.3: Safety endpoints and functional outcome after intravenous thrombolysis in patients with ischaemic strokes and stroke mimics

<table>
<thead>
<tr>
<th></th>
<th>Stroke mimics n=100 (%)</th>
<th>95% CI</th>
<th>Strokes n=5418 (%)</th>
<th>95% CI</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH&lt;sub&gt;NINDS&lt;/sub&gt;</td>
<td>2/99 (2.0)</td>
<td>0.3–7.1</td>
<td>403/5077 (7.9)</td>
<td>7.2–8.7</td>
<td>0.030</td>
</tr>
<tr>
<td>SICH&lt;sub&gt;ECASS-II&lt;/sub&gt;</td>
<td>1/100 (1.0)</td>
<td>0.0–5.0</td>
<td>275/4995 (5.5)</td>
<td>4.9–6.1</td>
<td>0.049</td>
</tr>
<tr>
<td>Fatal ICH</td>
<td>0/99 (0.0)</td>
<td>0–3.7</td>
<td>125/4699 (2.7)</td>
<td>2.2–3.1</td>
<td>0.115†</td>
</tr>
<tr>
<td>Mortality</td>
<td>2/96 (2.1)</td>
<td>0.3–7.3</td>
<td>766/5327 (14.4)</td>
<td>13.4–15.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mRs 0–1</td>
<td>72/96 (75.0)</td>
<td>65.1–83.3</td>
<td>2106/5327 (39.5)</td>
<td>38.2–40.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mRs 0–2</td>
<td>84/96 (87.5)</td>
<td>79.2–93.4</td>
<td>2958/5327 (55.5)</td>
<td>54.2–56.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Orolingual edema</td>
<td>0/49 (0.0)</td>
<td>0–7.4</td>
<td>25/2493 (1.0)</td>
<td>0.1–1.5</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* χ² test unless stated otherwise; †Fisher exact test.

CI indicates confidence interval; ECASS-II, European Cooperative Acute Stroke Study II; ICH, intracranial haemorrhage; NINDS, National Institutes of Neurological Diseases and Stroke; mRs, modified Rankin scale; SICH, symptomatic intracranial haemorrhage.

Safety and outcome of stroke mimics

One patient (1%, 95% CI 0.0–5.0) had a SICH<sub>ECASS-II</sub>. This was a 76-year-old man, finally diagnosed with an epileptic seizure, who had an SICH causing hemianopia with a favourable outcome. Another 73-year-old man who presented with an epileptic seizure due to an old postoperative defect experienced SICH<sub>NINDS</sub> with an excellent outcome. Compared with strokes, the rate of SICH according to any of the definitions was lower in stroke mimics, whereas only fatal ICH did not reach statistical significance since no fatal ICH occurred in stroke mimics. There were no cases of orolingual edema in stroke mimics (Table 6.3).

Three-month follow-up data were complete in 98.3% (96 stroke mimics, 5473 strokes). Mortality in stroke mimics was lower compared to strokes: 2.0% versus 14.4% (p<0.0001, Table 6.3). Among the two stroke mimics who died was an 86-year-old man with an epileptic seizure with a sudden death two weeks before the 3-months visit. The other stroke mimic died because of a brain tumour at the age of 75. Stroke mimics had more often favourable outcome (87.5% versus 55.5%) and excellent outcome at 3 months (75.0% versus 39.5%, both p<0.0001).
Literature search
Our search strategy yielded 99 hits. These included ten studies describing 219 stroke mimics in a total of 3916 patients treated with IVT \(^{6-15}\) and another five case reports.\(^{24-28}\) Patients from three studies (28 stroke mimics, 1695 strokes) are included in this study.\(^{6,7,14}\) All studies were conducted in tertiary care settings. Three studies included satellite hospitals as well.\(^{10,11,13}\) Stroke mimics were retrospectively identified from hospital-based stroke registers in all studies but one.\(^{11}\) Definitions of stroke mimics used and results of the studies are summarized in Table 6.4. Studies univocally suggested that IVT in stroke mimics was safe. No SICH was reported and only one patient with a stroke mimic died within 3 months after IVT.\(^7\) This patient was included in our study. One case report described a SICH in a patient with a glioblastoma multiforme.\(^{24}\)

DISCUSSION
This multicenter consecutive cohort study shows that the proportion of patients with a stroke mimic treated with IVT is small. Our study suggests that IVT in stroke mimics is safe since the rate of symptomatic intracranial haemorrhage was low and incidental death was not attributed to IVT. This is the largest study of stroke mimics in a consecutive IVT cohort to date. Our rate of 1.8% is in the lower range of the 1.4–15.5% reported in previous studies.\(^{6-15}\) This low rate can be explained by the definition of stroke mimics used in this study. The aim of our study was to report on IVT treatment in patients retrospectively diagnosed as stroke mimics under real-life conditions from a large and heterogeneous population treated with IVT. This pragmatic definition and the retrospective design is a limitation of our study that might have introduced a potential bias of underreporting of stroke mimic. If we had applied a more strict and uniform definition, including a MRI with DWI in each patient before or directly after IVT, likely more patients would be diagnosed as stroke mimic, since negative MRI would raise the suspicion of a stroke mimic. However, stroke remains a clinical diagnosis and MRI is still not performed as standard care in acute stroke care due to limited availability and several contraindications. In this study, only two of twelve centres routinely perform MRI before IVT and an-
Table 6.4: Studies reporting on stroke mimics treated with IVT from the literature

<table>
<thead>
<tr>
<th>Registry</th>
<th>IVT</th>
<th>Stroke mimics, ( n(%) )</th>
<th>Definition of stroke mimics</th>
<th>Age, median</th>
<th>Men, %</th>
<th>NIHSS, median</th>
<th>Follow-up</th>
<th>SICH, %</th>
<th>Mortality, %</th>
<th>mRs 0-1, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan(^{41})</td>
<td>151</td>
<td>6 (4.0)</td>
<td>Alternate clinical discharge diagnosis</td>
<td>39</td>
<td>-</td>
<td>14</td>
<td>discharge</td>
<td>0.0</td>
<td>0.0</td>
<td>16.7</td>
</tr>
<tr>
<td>Basel(^{44})</td>
<td>250</td>
<td>7 (2.8)</td>
<td>Absence of ischaemic lesions on post-IVT imaging and alternate clinical diagnosis</td>
<td>68 †</td>
<td>57</td>
<td>9</td>
<td>3 months</td>
<td>0.0</td>
<td>0.0</td>
<td>85.7</td>
</tr>
<tr>
<td>Pittsburgh(^{51})</td>
<td>254</td>
<td>9 (3.5)</td>
<td>Persistent symptoms with absent ischaemic lesions on post-IVT MR-DWI or cerebral ischaemia considered unlikely in transient symptoms</td>
<td>49</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Houston(^{8})</td>
<td>512</td>
<td>69 (14.0)</td>
<td>Absence of ischaemic lesions on post-IVT MR-DWI and alternate clinical diagnosis</td>
<td>55 †</td>
<td>40</td>
<td>7</td>
<td>discharge</td>
<td>0.0</td>
<td>0.0</td>
<td>87.0</td>
</tr>
<tr>
<td>Memphis(^{50})</td>
<td>89†</td>
<td>9 (10.1)</td>
<td>Clinical presentation, hospital course and absence of ischaemic lesions on post-IVT MR-DWI</td>
<td>52 †</td>
<td>45</td>
<td>6</td>
<td>-</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lille + Belgrade(^{7,*})</td>
<td>488</td>
<td>7 (1.4)</td>
<td>Absence of ischaemic lesions on post-IVT imaging and alternate clinical diagnosis</td>
<td>46</td>
<td>57</td>
<td>7</td>
<td>3 months</td>
<td>0.0</td>
<td>14.0</td>
<td>71.4</td>
</tr>
<tr>
<td>Phoenix(^{12,*})</td>
<td>539</td>
<td>56 (10.4)</td>
<td>Absence of ischaemic lesions on post-IVT MR-DWI and alternate clinical discharge diagnosis</td>
<td>56 †</td>
<td>45</td>
<td>6</td>
<td>discharge</td>
<td>0.0</td>
<td>-</td>
<td>96.0</td>
</tr>
<tr>
<td>Phoenix(^{15,*})</td>
<td>193</td>
<td>30 (15.5)</td>
<td>Absence of ischaemic lesions on post-IVT MR-DWI and alternate clinical diagnosis</td>
<td>56 †</td>
<td>-</td>
<td>6</td>
<td>discharge</td>
<td>0.0</td>
<td>0.0</td>
<td>87.0(|)</td>
</tr>
<tr>
<td>Helsinki(^{6,*})</td>
<td>985</td>
<td>14 (1.4)</td>
<td>Absence of ischaemic lesions on post-IVT imaging and alternate clinical diagnosis</td>
<td>56</td>
<td>21</td>
<td>8</td>
<td>3 months</td>
<td>0.0</td>
<td>0.0</td>
<td>69.2</td>
</tr>
<tr>
<td>Mannheim(^{9})</td>
<td>648</td>
<td>42 (6.5)</td>
<td>Absence of ischaemic lesions on post-IVT MR-DWI and alternate clinical diagnosis</td>
<td>61 †</td>
<td>21</td>
<td>6.5</td>
<td>discharge</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
</tr>
</tbody>
</table>

* patients were included in this study as well; † mean age; ‡ data including patients with transient ischaemic attacks \( n=14 \); § overlap of patients between studies; ¶ proportion of patients with mRs scores of 0–2 instead of 0–1.
IVT indicates intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; SICH, symptomatic intracranial haemorrhage; mRs, modified Rankin scale; MR-DWI, magnetic resonance diffusion-weighted imaging.
other five multimodal computed tomography (CT) imaging. Although superior to noncontrast CT for the diagnosis of acute ischaemic stroke, MRI still has a false negative rate of 17% (27% in patients presenting within 3 hours after symptom onset), which might falsely increase the proportion of patients with a stroke mimic. This percentage however decreases when localizing clinical information is provided.

Another explanation of our low proportion could be that our study was performed in experienced stroke centres where patients were evaluated by (stroke) neurologists. This is in contrast to some community hospitals where emergency physicians start IVT after telephone consultation with a (stroke) neurologist. Indeed, IVT stroke mimics identified by negative MRI were more likely to be treated with IVT in a community hospital compared to a stroke center. On average, with half of the centres using noncontrast CT in the acute phase, our mimics rate of 1.8% is right between the 3% target, which is proposed for centres using noncontrast CT alone, and the 1% target, which is recommended for centres using multimodal imaging.

In an ideal situation, stroke mimics would not be treated with IVT. However, in centres where only noncontrast CT is routinely performed prior to the administration of IVT, additional multimodal imaging is often at the expense of early treatment onset and thereby beneficial outcome in patients with acute ischaemic stroke. Results from the recent International Stroke Trial 3 confirmed once more that stroke patients benefit most from early start of IVT. Our largest data set of stroke mimics treated with IVT adds to the current knowledge on IVT in stroke mimics that previous assumptions hold and our study provides no evidence to change current practice. Putting our findings in this context, it seems reasonable to start IVT and continue with more sophisticated diagnostics test during treatment in uncertain cases. However, time delays due to imaging of the vessel status and brain perfusion is getting shorter with modern multimodal imaging techniques and are increasingly incorporated into routine imaging protocols before IVT.

In conclusion, among patients treated with IVT in experienced stroke centres, only few had a final diagnosis other than stroke and the complication rate in these stroke mimics was low. In our opinion, whereas efforts should be made to
avoid IVT in such patients, rapid treatment is likely more beneficial than adding extensive exams to rule out mimics in daily clinical practice.

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REFERENCES


