Off-Label Thrombolysis for Acute Ischemic Stroke: Rate, Clinical Outcome and Safety Are Influenced by the Definition of ‘Minor Stroke’

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Key Words
Acute ischemic stroke · Thrombolysis · Off-label use · Minor stroke

Abstract
Background: Several contraindications for intravenous thrombolysis are not based on controlled trials. Specialized stroke centers often apply less restrictive criteria. The aim of our study was to analyze how many patients at our institution receive off-label thrombolysis. In addition, clinical outcome and safety data were compared to those from patients treated on-label, and the influence of different definitions of ‘minor stroke’ were examined. Methods: Consecutive thrombolysis patients treated between January 2006 and January 2010 were included. Patients treated off-label were compared to patients given on-label therapy according to the European license. Since no specified definition for ‘minor neurological deficit’ exists in the license, two distinct definitions were considered off-label, i.e. National Institutes of Health Stroke Scale score (NIHSSS) <1 (definition 1) and NIHSSS ≤4 (definition 2). Results: Of a total of 422 patients, 232 (55%) were treated off-label. The most prevalent off-label criteria (OLCs) were the following: age >80 years (n = 113), minor stroke (definition 1, n = 3; definition 2, n = 84), elevated blood pressure necessitating aggressive treatment (n = 75), time window >3 h (n = 71) and major surgery or trauma within the preceding 3 months (n = 20). In group comparisons, off-label patients had an overall worse outcome using definition 1 for minor stroke, while there was no difference when definition 2 was applied. In multivariate analysis, off-label therapy (definition 1) in general and age >80 years were independent predictors of poor outcome. None of the contraindications were associated with an increased bleeding risk. Conclusions: Off-label therapy is frequently applied at our center and is not associated with higher complication rates. Overall outcome of off-label treatment largely depends on the definition used for minor stroke. Besides age >80 years, a known poor prognostic factor, no other specific OLC was associated with poor outcome. Our data suggest that the criteria in the European license may be too restrictive.

Introduction

Multiple contraindications for thrombolysis with tissue plasminogen activator (tPA) have hampered the wider use of this therapy for patients with acute ischemic stroke. Several of those contraindications have not been
systematically studied and are not directly derived from the inclusion and exclusion criteria of the pivotal and approval-relevant randomized controlled trials. On the contrary, they were introduced on the basis of subgroup analyses or even expert opinions to putatively maximize the safety of the treatment in the initial phase of clinical implementation and thus might be overrestrictive for further clinical use. In addition, existing guidelines as well as official licenses vary in different parts of the world. For instance, influenced by the early European Cooperative Acute Stroke Study (ECASS) trials [1, 2], an upper age limit of 80 years for thrombolysis in Europe was defined, while no such limit exists in the USA. There are few data available on the outcome and safety of treatment in the case of the various off-label criteria (OLCs). Based on increasing clinical experience and several observational studies, an increasing number of experienced stroke centers follow their own less restrictive thrombolysis protocols rather than adhering rigidly to the official licenses for tPA [3, 4]. The aim of our study was to analyze how many patients at our institution receive off-label thrombolysis according to the European license. Furthermore, clinical outcome and safety data [intracerebral hemorrhage (ICH) rates] were compared to those of patients treated on-label, and the influence of different definitions of ‘minor stroke’ in this context were examined.

Materials and Methods

The Erlangen Stroke and Thrombolysis Database is a prospective database of all patients with acute ischemic stroke treated at our institution (University Hospital Erlangen, Germany). It contains baseline demographic and stroke-related data as well as treatment specifics, imaging information and outcome parameters for each stroke patient. Outcome at day 90 was assessed using the Modified Rankin Scale (mRS) evaluated by a neurologist as part of the general database independently from the present study using a semistructured interview either in person or by telephone. Favorable clinical outcome was defined as mRS 0–2 and/or clinical recovery to the prestroke mRS. Four patients were lost to follow-up at day 90. Asymptomatic ICH and symptomatic ICH (sICH) were defined according to the ECASS-3 criteria [5].

Study Population

For this study, we extracted data for all patients with acute ischemic stroke from this database who received intravenous thrombolysis (IVT) in our institution between January 2006 and January 2010. All patients with basilar artery occlusion and all patients who received either intra-arterial thrombolysis or combined intra-arterial thrombolysis/IVT (bridging) were excluded. Our institutional guidelines are less restrictive than the European Medicines Agency license for tPA (see table 1 for a detailed protocol). Treatment within 3 h (4.5 h according to ECASS-3) is based on noncontrast CT only, while treatment in an extended time window is based on MRI criteria as described previously [6]. Patients treated off-label were identified, and outcome and safety data were compared to those of patients who received on-label therapy. Since no specified definition of ‘minor neurological deficit’ is given in the European or US license for tPA, two distinct definitions were considered ‘off-label’ for the purposes of this study: National Institutes of Health Stroke Scale score (NIHSSS) <1 on admission (definition 1), and NIHSSS ≤4 on admission (definition 2).

All patients were treated and monitored at our stroke unit according to European guidelines [7]. All patients received either CT or MRI at 24–36 h to evaluate hemorrhagic complications. Informed consent was obtained from the patient or next of kin in the case of off-label IVT in any case, and the thrombolysis protocol was approved by our institutional ethics committee.

Statistical Analysis

Statistical analyses were performed using the ‘SPSS’ software package (version 18.0, SSPS Inc.). All data were tested for normality and are given as medians and range or means and SD, as appropriate. Categorical variables are presented as frequencies and percentages. The groups of on- and off-label patients were compared using the Mann-Whitney U test, $\chi^2$ test and Fisher’s exact test. Multivariate regression analyses were performed separately for poor clinical outcome, sICH and mortality using a backward stepwise regression model. For each OLC demonstrating at least a trend (p < 0.1) with regard to the chosen end point in univariate analysis, a separate model was calculated introducing established predictors (age, NIHSSS at baseline) for the outcome and safety of thrombolysis. In addition, all models were adjusted for baseline variables. For all analyses, a 2-tailed p value ≤0.05 was considered statistically significant.

Results

Baseline Characteristics

Between January 2006 and January 2010, a total of 422 patients received IVT. Baseline characteristics of all patients and comparison of on- and off-label thrombolysis using the two different definitions for minor strokes are shown in table 2. Independently of the definition used, patients treated off-label were older, had higher blood pressure on hospital admission and were more likely to have a history of arterial hypertension, atrial fibrillation and previous strokes. The rate of cardioembolic strokes was higher and the time window (symptom to needle time) was longer in the off-label groups.

Off-Label Thrombolysis

Overall, 232 of 422 IVT patients (55%) received off-label thrombolysis according to definition 1 (minor stroke = NIHSSS = 0) and 270 (64%) according to definition 2 (minor stroke = NIHSSS ≤ 4). The annualized rates
Table 1. Off-label criteria according to the European Medicines Agency (2002), our institutional approach and the rate of individual contraindications in our cohort (n = 422)

<table>
<thead>
<tr>
<th>Contraindications as per European Medicines Agency license</th>
<th>Applied at our institution</th>
<th>Treatment guideline for intravenous thrombolysis at our institution</th>
<th>Rate of individual contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;18 years, &gt;80 years</td>
<td>no</td>
<td>patients &gt;80 years are treated; patients &lt;18 years are treated at the Pediatrics Department and were not included in this study</td>
<td>113 26.8</td>
</tr>
<tr>
<td>Intravenous treatment of blood pressure</td>
<td>no</td>
<td>patients with elevated blood pressure receive intravenous treatment before thrombolysis</td>
<td>75 17.9</td>
</tr>
<tr>
<td>Blood pressure &gt;185 mm Hg</td>
<td>(yes)</td>
<td>patients are treated up to 4.5 h according to ECASS-3 criteria, otherwise treatment &gt;3 h is based on MRI selection criteria</td>
<td>71 17.4</td>
</tr>
<tr>
<td>Symptom to needle time &gt;3 h</td>
<td>no</td>
<td>patients are treated up to an INR of ≤1.7</td>
<td>22 5.2</td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>(yes)</td>
<td>patients are treated up to an INR of ≤1.7</td>
<td>22 5.2</td>
</tr>
<tr>
<td>Major surgery &lt;3 months</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Significant trauma &lt;3 months</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Serious head trauma</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Previous stroke and diabetes</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Severe stroke (NIHSSS on admission &gt;25)</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Previous stroke &lt;3 months</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Minor neurological deficit (defined as NIHSSS = 0)</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Minor neurological deficit (defined as NIHSSS ≤4)</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Platelet count &lt;100 × 10^3/µl</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Bacterial endocarditis, pericarditis</td>
<td>yes</td>
<td>no ultrasound screening for endocarditis or pericarditis is applied</td>
<td>1 0.2</td>
</tr>
<tr>
<td>Rapidly improving symptoms</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Glucose &lt;50 mg/dl, &gt;400 mg/dl</td>
<td>no</td>
<td>no patients are treated only if imaging shows subacute infarction</td>
<td>4 0.9</td>
</tr>
<tr>
<td>Epileptic seizure at onset</td>
<td>no</td>
<td>once diagnosis is confirmed (additional imaging)</td>
<td>– –</td>
</tr>
<tr>
<td>History of intracranial neoplasm, AVM or aneurysm</td>
<td>no</td>
<td>individual decision by the treating physician</td>
<td>– –</td>
</tr>
<tr>
<td>Intracranial or spinal surgery</td>
<td>no</td>
<td>individual decision by the treating physician</td>
<td>– –</td>
</tr>
<tr>
<td>History of intracranial hemorrhage</td>
<td>no</td>
<td>individual decision by the treating physician</td>
<td>– –</td>
</tr>
<tr>
<td>History of SAH from aneurysm</td>
<td>no</td>
<td>individual decision by the treating physician</td>
<td>– –</td>
</tr>
<tr>
<td>ICH on CT</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Suspected SAH even if imaging normal</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Severe stroke on imaging (&gt;1/3 MCA territory)</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Heparin/LMWH with high APTT</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Current bleeding diathesis</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Neoplasms with increased bleeding risk</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Traumatic external heart massage &lt;10 days</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Puncture of noncompressible blood vessel &lt;10 days</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Obstetric delivery &lt;10 days</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Ulcerative gastrointestinal disease</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>yes</td>
<td>– –</td>
<td>– –</td>
</tr>
</tbody>
</table>

AVM = Arteriovenous malformation; SAH = subarachnoid hemorrhage; MCA = middle cerebral artery; LMWH = low-molecular weight heparin; APTT = activated partial prothrombin time; INR = International Normalized Ratio.
of off-label thrombolysis for the period between January 2006 and January 2010 are given in figure 1. The rate of off-label treatment did not change significantly over the examined years. The most frequent OLCs were age >80 years (n = 113, 26.8%), blood pressure >185/110 mm Hg combined with intravenous use of antihypertensives before treatment (n = 75, 17.9%), symptom onset to needle time >3 h (n = 71, 17.4%) and major surgery or severe trauma within the preceding 3 months (n = 20, 4.7%). Information on all individual license contraindications is shown in table 1. Several of the other European Medicines Agency contraindications listed in table 1 did not occur in our study population, e.g. age <18 years (this patient group is by definition treated at the Pediatrics Department at our institution), epileptic seizure at stroke onset and glucose level at admission <50 or >400 mg/dl. Depending on the definition used, there is a clear difference in the number of minor strokes; thus, using defi-
Of the 422 patients, 159 (37.7%) had 1 contraindication for thrombolytic therapy (using definition 1), 61 patients
(14.5%) had 2 and 11 patients (2.6%) had 3 concomitant OLCs. In 1 patient (0.2%), 4 OLCs (age >80 years, blood pressure >185/110 mm Hg and/or use of intravenous antihypertensives, previous stroke and diabetes, current therapy with anticoagulants) were found by the time of thrombolysis (no sICH, mRS of 3 at 90 days). Regression analysis regarding outcome and sICH depending on the number of coexisting OLCs (using definition 1) demonstrated an increasing OR for poor clinical outcome the more contraindications were present, whereas no such relation existed for sICH. The OR for poor clinical outcome at 3 months for 1 OLC was 2.04 (95% CI 1.32–3.14; p = 0.001), which increased to 2.85 (95% CI 1.57–5.18; p = 0.001) with 2 coexisting OLCs and 16.08 (95% CI 2.02–128.21; p = 0.009) with 3 OLCs.

### Discussion

Experienced stroke centers use tPA beyond existing license restrictions but few data are available on the outcome and safety of off-label thrombolysis. Several studies have focussed on individual OLCs but only few publications have addressed outcome and safety with tPA contraindications in general [3, 8, 9]. We analyzed how many patients in our institution received off-label thrombolysis according to the European product license and compared their clinical outcome and safety data to those of patients treated on-label.

Overall, 55% of our thrombolysis patients would not have been treated if we had adhered strictly to the European product license for tPA. As a direct consequence of

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**Table 3. Outcome and safety parameters of all patients (n = 422) comparing on- and off-label thrombolysis using different off-label definitions**

<table>
<thead>
<tr>
<th>Outcome at 3 months</th>
<th>All patients (n = 422; 100%)</th>
<th>Off-label definition 1(^a) (n = 232; 55%)</th>
<th>On-label definition 1(^a) (n = 190; 45%)</th>
<th>p value definition 1(^a)</th>
<th>Off-label definition 2(^b) (n = 270; 64%)</th>
<th>On-label definition 2(^b) (n = 152; 36%)</th>
<th>p value definition 2(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good clinical outcome(^c)</td>
<td>209 (50)</td>
<td>91 (39.7)</td>
<td>118 (62.4)</td>
<td><strong>0.000</strong></td>
<td>129 (48.1)</td>
<td>80 (53.3)</td>
<td>0.308</td>
</tr>
<tr>
<td>Mortality(^c)</td>
<td>49 (11.7)</td>
<td>34 (14.8)</td>
<td>15 (7.9)</td>
<td><strong>0.032</strong></td>
<td>34 (12.7)</td>
<td>15 (10)</td>
<td>0.433</td>
</tr>
<tr>
<td>Hemorrhagic complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aICH</td>
<td>29 (6.6)</td>
<td>19 (8.2)</td>
<td>10 (5.3)</td>
<td>0.237</td>
<td>20 (7.4)</td>
<td>9 (6)</td>
<td>0.580</td>
</tr>
<tr>
<td>sICH</td>
<td>15 (3.6)</td>
<td>9 (3.9)</td>
<td>6 (3.2)</td>
<td>0.690</td>
<td>9 (4.0)</td>
<td>6 (3.3)</td>
<td>0.729</td>
</tr>
</tbody>
</table>

Values represent numbers of patients with percentages in parentheses. aICH = Asymptomatic ICH. p values in bold are significant.

\(^a\) Definition 1: NIHSSS <1 on admission, i.e. minor stroke = NIHSSS = 0.

\(^b\) Definition 2: NIHSSS ≤4 on admission, i.e. minor stroke = NIHSSS ≤4.

\(^c\) Four patients were lost to follow-up at day 90 (3 off-label and 1 on-label using definition 1 for mild stroke; 2 patients in each group using definition 2).

**Table 4. Impact of separate OLCs in multivariate regression analysis**

<table>
<thead>
<tr>
<th>Poor clinical outcome</th>
<th>Mortality</th>
<th>sICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-label therapy</td>
<td>2.56 (1.62–4.06)</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>1.94 (1.16–3.26)</td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td>Previous stroke and diabetes</td>
<td>5.12 (0.54–49.05)</td>
<td>0.157</td>
</tr>
<tr>
<td>NIHSSS &gt;25</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Previous stroke ≤3 months</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

For each OLC, a separate model for all outcome end points was calculated. Each model was adjusted for baseline characteristics and for factors showing a trend in univariate analysis. p values in bold are significant.
ignoring the respective license restrictions, off-label pa-
patients were older, arrived more often within an extended
time window, had higher blood pressure on hospital ad-
mission and were more likely to have a history of arterial
hypertension and previous strokes. Higher rates of previ-
ous atrial fibrillation and cardioembolic strokes among
the off-label patients are probably related to the higher
age in this subgroup (table 2).

In general, license restrictions can be divided into two
distinct groups. The first group excludes patients with a
presumed favorable outcome – mainly patients with mild
strokes – in whom the risks of treatment might exceed the
potential benefit. The second group of restrictions aim to
avoid treatment in patients with an elevated risk of com-
lications (i.e. patients >80 years). In an analysis that
combines both of these groups as ‘off-label’, the first
group may partly compensate for worse outcome effects
driven by the second group. Therefore, the definition of
‘minor stroke’ is of particular importance. Neither inter-
national guidelines [7, 10] nor European or Food and
Drug Administration licenses give an exact definition of
the term ‘minor stroke’. The wording in the license relates
to the inclusion criteria of the approval-relevant National
Institute of Neurological Disorders and Stroke trial,
which enrolled patients with an NIHSSS of at least 1 [11].
However, a multitude of different definitions are used in
the literature, with the most commonly used threshold
being an NIHSSS of ≤4 [12–18]. Therefore, we used both
definitions of minor stroke in this study to directly ana-
lyze their effect on outcome and sICH rates between pa-
tients treated on- and off-label.

Considering patients with an initial NIHSSS of ≤4 as
off-label, there was no statistically significant difference
in the number of patients who achieved a good clinical
outcome between patients treated off- and on-label. This
corresponds well with the results presented by Meretoja
et al. [3], who recently compared outcome and ICH rates
in patients treated with off-label and on-label IVT using
the same definition for minor stroke. In addition, apply-
ing this definition in our study, the favorable outcome in
our off-label patients (48.1%) was comparable to that in
the above-mentioned study (54.5%) [3]. In contrast, de-
fining only NIHSSS <1 as off-label and thus shifting pa-
tients with an NIHSSS of 1–4 to the on-label group natu-
rally reduces the rate of favorable outcomes in the off-
label group (39.7%). At the same time, it ‘improves’
outcome in the on-label population. This shift leads to an
overall significantly worse outcome in the off-label com-
pared to on-label patients and underlines the hypothesis
that including mild strokes in the cohort of all off-label
patients can lead to a serious bias of the overall off-label
outcome.

In our cohort, age >80 years was not only the most
common OLC but also the only specific independent pre-
dictor for poor outcome in multivariate regression analy-

sis. Among the OLCs, age >80 years is the best examined
predictor for outcome. Recently, Rubiera et al. [4] com-
pared patients treated according to Safe Implementation
of Thrombolysis in Stroke-Monitoring Study criteria
with patients not fulfilling those criteria. They also iden-
tified age >80 years as the most important factor for
worse outcome in off-label patients. Exclusion of patients
>80 years led to comparable outcomes in both groups.
The finding that thrombolysed patients >80 years have a
worse outcome was shown in many previous studies [19–
24]. However, this is expected since age is one of the most
important outcome predictors for stroke patients irre-
pective of tPA treatment and therefore should not lead
to the assumption that IVT is not beneficial in this patient
subgroup. This is also supported by recent analyses of pa-
tients from the Virtual International Stroke Trials Ar-
chive and Safe Implementation of Treatments in Stroke
databases [25], and ongoing trials such as the Third In-
ternational Stroke Trial and the Thrombolysis in Elderly
Stroke Patients in Italy multicenter trial will soon address
this issue.

In concordance with the previously mentioned studi-
es, our data did not reveal significant differences in sICH
rates between on- and off-label patients independently
of the off-label definition used. Though age >80 years,
NIHSSS ≥25 and previous stroke showed a trend, none of
the specific license contraindications were significantly
associated with a higher rate of sICH.

Even though one isolated contraindication might not
seriously affect the outcome of IVT patients, there are few
data on the influence of multiple concomitant OLCs in a
single patient. In our study, the OR for poor clinical out-
come but not for sICH increased with the number of con-
comitant contraindications. It doubled in patients with 1
OLC compared to on-label patients and almost tripled
when 2 OLCs were present. In patients with 3 OLCs, it
increased up to 16-fold. Although the number of patients
with 3 OLCs is small and this effect might be overesti-
imated, our results indicate that patients with 2 or more
concomitant OLCs should be treated with caution.

Our study has limitations, most notably the single-
center approach and the retrospective design. However,
to the best of our knowledge it is the first study to analyze
the effect of different definitions of minor stroke on out-
come and safety in patients given off-label thrombolysis.

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Stroke

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In conclusion, off-label therapy is frequently applied at our center and is not associated with higher complication rates. More than half of our patients would not have been treated if we had strictly followed the European license. An exact definition of individual contraindications (particularly ‘minor stroke’) is essential to evaluate the clinical outcome of patients treated off-label and to compare the results of different studies. Beside age >80 years, a known poor prognostic factor in stroke patients in general, no specific OLC was associated with poor outcome. Our data suggest that the criteria in the European tPA license might be too restrictive.

Disclosure Statement

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