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 (NIHSS) <1 (definition 1) and NIHSS ≤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.

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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 (NIHSS) <1 on admission (definition 1), and NIHSS ≤ 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, χ^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, NIHSS 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 = NIHSS = 0) and 270 (64%) according to definition 2 (minor stroke = NIHSS ≤ 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)

Contraindications as per European Medicines Agency license	Applied at our institution	Treatment guideline for intravenous thrombolysis at our institution	Rate of individual contraindications	
			n	%
Age <18 years, >80 years	no	patients >80 years are treated; patients <18 years are treated at the Pediatrics Department and were not included in this study	113	26.8
Intravenous treatment of blood pressure	no	patients with elevated blood pressure receive intravenous treatment before thrombolysis	75	17.9
Blood pressure >185 mm Hg	(yes)			
Symptom to needle time >3 h	no	patients are treated up to 4.5 h according to ECASS-3 criteria, otherwise treatment >3 h is based on MRI selection criteria	71	17.4
Oral anticoagulation	(yes)	patients are treated up to an INR of ≤ 1.7	22	5.2
Major surgery <3 months	no	individual decision by the treating physician		
Significant trauma <3 months	no		20	4.7
Serious head trauma <3 months	no			
Previous stroke and diabetes	no		9	2.1
Severe stroke (NIHSSS on admission >25)	no		5	1.2
Previous stroke <3 months	no	patients are not treated only if imaging shows subacute infarction	4	0.9
Minor neurological deficit (defined as NIHSSS = 0)	no	functionally disabling symptoms are treated regardless of the NIHSSS; decision can also be based on imaging information	3	0.7
Minor neurological deficit (defined as NIHSSS ≤ 4)	no	functionally disabling symptoms are treated regardless of the NIHSSS; decision can also be based on imaging information	84	19.9
Platelet count <100 $\times 10^3/\mu\text{l}$	no	patients are usually treated with tPA before the laboratory results are available (except point-of-care testing of blood glucose and INR)	2	0.5
Bacterial endocarditis, pericarditis	yes	no ultrasound screening for endocarditis or pericarditis is applied	1	0.2
Rapidly improving symptoms	no	patients are treated once a functionally disabling deficit is detected irrespective of the development of the NIHSSS	–	–
Glucose <50 mg/dl, >400 mg/dl	no	patients are treated after treatment of very low and very high values of blood glucose	–	–
Epileptic seizure at onset	no	once diagnosis is confirmed (additional imaging)	–	–
History of intracranial neoplasm, AVM or aneurysm	no	individual decision by the treating physician	–	–
Intracranial or spinal surgery	no	individual decision by the treating physician	–	–
History of intracranial hemorrhage	no	individual decision by the treating physician	–	–
History of SAH from aneurysm	no	individual decision by the treating physician	–	–
ICH on CT	yes		–	–
Suspected SAH even if imaging normal	yes		–	–
Severe stroke on imaging (>1/3 MCA territory)	yes		–	–
Heparin/LMWH with high APTT	yes		–	–
Current bleeding diathesis	yes		–	–
Neoplasms with increased bleeding risk	yes		–	–
Traumatic external heart massage <10 days	yes		–	–
Puncture of noncompressible blood vessel <10 days	yes		–	–
Obstetric delivery <10 days	yes		–	–
Ulcerative gastrointestinal disease	yes		–	–
Esophageal varices	yes		–	–
Acute pancreatitis	yes		–	–
Severe liver disease	yes		–	–

AVM = Arteriovenous malformation; SAH = subarachnoid hemorrhage; MCA = middle cerebral artery; LMWH = low-molecular weight heparin; APTT = activated partial prothrombin time; INR = International Normalized Ratio.

Table 2. Baseline characteristics of all patients (n = 422) comparing on- and off-label thrombolysis using different off-label definitions

	All patients (n = 422; 100%)	Off-label definition 1 ^a (n = 232; 55%)	On-label definition 1 ^a (n = 190; 45%)	p value definition 1 ^a	Off-label definition 2 ^b (n = 270; 64%)	On-label definition 2 ^b (n = 152; 36%)	p value definition 2 ^b
Age, years	73 (63–81)	79 (69–84)	67 (58–75)	0.000	77 (66–84)	68 (60–75)	0.000
Males, n	233 (55.2)	115 (49.6)	118 (62.1)	0.010	142 (52.4)	91 (60.3)	0.119
Risk factors, n							
Hypertension	351 (83.2)	205 (88.4)	146 (76.8)	0.002	238 (87.8)	113 (74.8)	0.001
Hypercholesterolemia	229 (54.3)	116 (50)	113 (59.5)	0.052	143 (52.8)	86 (57)	0.408
Diabetes	146 (34.6)	81 (34.9)	65 (34.2)	0.880	93 (34.3)	53 (35.1)	0.871
Coronary artery disease	103 (24.5)	57 (24.2)	46 (24.2)	0.892	68 (25.3)	35 (23.2)	0.631
Atrial fibrillation	179 (42.4)	129 (55.6)	50 (26.3)	<0.001	131 (48.3)	48 (31.8)	0.001
Previous stroke	72 (17.1)	50 (21.6)	22 (11.6)	0.006	55 (20.4)	17 (11.3)	0.017
Nicotine	54 (12.8)	24 (10.3)	30 (15.8)	0.096	31 (11.4)	23 (15.2)	0.264
Previous myocardial infarction	42 (10.0)	23 (10.1)	19 (10)	0.988	25 (9.3)	17 (11.3)	0.512
Peripheral artery disease	46 (10.9)	23 (10.1)	23 (12.1)	0.482	30 (11.1)	16 (10.6)	0.871
Systolic blood pressure, mm Hg	160 (145–177)	163 (148–186.5)	155 (140–170)	0.000	162 (147–185)	153 (139–170)	0.000
Diastolic blood pressure, mm Hg	88 (77–100)	90 (78–100)	85 (75–95)	0.002	90 (79–100)	85 (75–92.5)	0.001
Temperature, °C	36.9 (36.5–37.3)	37.0 (36.5–37.3)	36.9 (36.5–37.3)	0.776	37.0 (36.5–37.3)	36.9 (36.5–37.3)	0.220
Laboratory parameters							
INR	1.02 (0.98–1.09)	1.05 (0.99–1.12)	1.0 (0.95–1.05)	0.000	1.04 (0.99–1.11)	1.00 (0.96–1.06)	0.000
Leukocytes, × 10 ³ /μl	8.5 (6.74–10.63)	8.6 (6.96–10.55)	8.3 (6.55–10.63)	0.213	8.5 (6.9–10.2)	8.5 (6.6–10.8)	0.696
Platelet count, × 10 ³ /μl	239 (197–298)	240 (201.5–299)	194 (198–298)	0.837	237 (197–292)	243 (197–301)	0.679
CRP, mg/l	4.8 (2.0–10.4)	5 (2.0–13.4)	3.85 (0.7–8.1)	0.001	5 (2–12)	4 (0.8–9)	0.031
Previous prophylactic treatment, n							
ASA	152 (36.4)	94 (40.9)	58 (30.9)	0.041	104 (38.8)	48 (32.0)	0.170
Clopidogrel	21 (5)	13 (5.7)	8 (4.3)	0.654	15 (5.6)	6 (4)	0.498
ER-DP/ASA	5 (1.2)	4 (1.7)	1 (0.5)	0.384	4 (1.5)	1 (0.7)	0.658
Oral anticoagulation	23 (5.5)	23 (10)	0	<0.001	23 (8.6)	0	0.000
No previous antiplatelet treatment	213 (50.5)	120 (63.8)	93 (40.4)	0.624	119 (44.4)	94 (62.7)	0.001
Glucose at baseline, mg/dl	114 (98–141)	117 (100–140)	110.5 (94–140)	0.114	113 (98–139)	113 (97–144)	0.626
Cholesterol at baseline, mg/dl	196.08 ± 45.7	191.3 ± 43.3	201.8 ± 47.6	0.022	197.7 ± 44.2	200.4 ± 48.3	0.152
NIHSS							
Baseline	9 (5–15)	9 (5–15)	8 (5–13)	0.039	8 (4–14)	10 (6–14)	0.005
After 24 h	6 (2–14)	6 (2–14)	4 (1–11)	0.002	5 (2–12)	6 (2–13)	0.493
At discharge	4 (1–11)	5 (1–12)	2 (0–9)	0.001	4 (1–11)	4 (1–10)	0.992
TOAST criteria, n							
Large vessel	30 (7.1)	12 (5.2)	18 (9.5)	0.127	18 (6.7)	12 (7.9)	0.694
Embolic	183 (43.4)	130 (56)	53 (28)	<0.001	135 (50)	48 (31.8)	0.000
Micro/lacunar	2 (0.5)	0	2 (1.1)	0.202	1 (0.4)	1 (0.7)	1.000
Other	23 (5.5)	8 (3.4)	15 (7.9)	0.001	10 (3.7)	13 (8.6)	0.044
Unknown	183 (43.4)	82 (35.3)	101 (53.4)	<0.001	106 (39.3)	77 (51)	0.025
Symptom to needle time, min	120 (90–180)	130 (90–210)	110 (85–150)	0.000	125 (90–195)	107.5 (85–150)	0.000

Values represent medians (interquartile ranges), numbers (percentages) or means ± SD, as appropriate. p values in bold are significant. INR = International Normalized Ratio; CRP = C-reactive protein; ASA = acetylsalicylic acid; ER-DP = extended release dipyridamole; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

^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.

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%). In-

formation 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 defini-

Fig. 1. Annual rates of on- and off-label thrombolysis for the years between January 2006 and January 2010. Front columns: using definition 1 (Def. 1) for minor strokes. Back columns: using definition 2 (Def. 2).

tion 1, minor stroke occurred in only 3 cases (0.7%), while using definition 2 resulted in 84 cases (19.9%).

Comparison of Clinical Outcome between Off- and On-Label Thrombolysis

Group comparison of clinical outcome between off- and on-label thrombolysis showed differing results depending on the definition of minor stroke within the off-label criteria. Using definition 1 (defining only NIHSS = 0 as off-label), there was a significant difference between these two groups, with fewer patients with a good clinical outcome in the off-label group (table 3). No such difference was present applying definition 2 (defining NIHSS ≤ 4 as off-label).

Since this difference was only apparent when definition 1 was used, we performed a multivariate regression analysis to detect independent predictors for poor outcome on this basis. Of all contraindications (using definition 1), age >80 years [odds ratio (OR) 2.34, 95% confidence interval (CI) 1.49–3.67; $p < 0.001$], previous stroke and diabetes (OR 8.28, 95% CI 1.03–66.79; $p = 0.047$) and off-label therapy in general (OR 2.52, 95% CI 1.70–3.74; $p < 0.001$) were relevant factors for poor clinical outcome in a univariate regression analysis. Age >80 years and off-label therapy were independent predictors in the multivariate regression model (adjusted for relevant baseline parameters) for poor outcome at day 90 (OR 1.94, 95% CI 1.16–3.24; $p = 0.012$, and OR 2.56, 95% CI 1.62–4.06; $p < 0.001$, respectively; table 4).

Comparison of Mortality between Off- and On-Label Thrombolysis

Results of group comparison for mortality in patients treated off- and on-label were similar to the analysis of clinical outcome. Using definition 1, the mortality rate in the off-label group was significantly higher than in the on-label group, while no such difference existed when using definition 2 (table 3). Though significantly associated in a univariate regression analysis, neither age >80 years nor off-label therapy in general were independent predictors for mortality in the multivariate regression analysis (table 4).

Comparison of sICH between Off- and On-Label Thrombolysis

Independently of the definition of minor stroke within the OLCs, there was no significant difference in the number of sICHs between on- and off-label patients (table 3).

For sICH, none of the license contraindications was revealed either as a relevant factor in the univariate regression analysis or as an independent predictor in the multivariate analysis. Even off-label thrombolysis in general was not significantly associated with a higher number of sICHs or poor outcome (table 4).

Outcome and Safety Depending on the Number of Concomitant OLCs

Of the 422 patients, 159 (37.7%) had 1 contraindication for thrombolytic therapy (using definition 1), 61 patients

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

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

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

	Poor clinical outcome		Mortality		sICH	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Off-label therapy	2.56 (1.62–4.06)	0.000	0.559 (0.167–1.871)	0.345	–	–
Age >80 years	1.94 (1.16–3.26)	0.012	0.714 (0.152–3.351)	0.669	2.49 (0.88–7.02)	0.086
Previous stroke and diabetes	5.12 (0.54–49.05)	0.157	–	–	–	–
NIHSSS >25	–	–	–	–	7.196 (0.76–68.63)	0.086
Previous stroke ≤3 months	–	–	–	–	9.619 (0.94–98.38)	0.056

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.

(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

ignoring the respective license restrictions, off-label patients were older, arrived more often within an extended time window, had higher blood pressure on hospital admission and were more likely to have a history of arterial hypertension and previous strokes. Higher rates of previous 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 complications (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 international 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 NIHSS of at least 1 [11]. However, a multitude of different definitions are used in the literature, with the most commonly used threshold being an NIHSS of ≤ 4 [12–18]. Therefore, we used both definitions of minor stroke in this study to directly analyze their effect on outcome and sICH rates between patients treated on- and off-label.

Considering patients with an initial NIHSS 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, applying 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, defining only NIHSS < 1 as off-label and thus shifting patients with an NIHSS of 1–4 to the on-label group naturally 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 compared 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 predictor for poor outcome in multivariate regression analysis. Among the OLCs, age >80 years is the best examined predictor for outcome. Recently, Rubiera et al. [4] compared patients treated according to Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria with patients not fulfilling those criteria. They also identified 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 irrespective 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 patients from the Virtual International Stroke Trials Archive and Safe Implementation of Treatments in Stroke databases [25], and ongoing trials such as the Third International Stroke Trial and the Thrombolysis in Elderly Stroke Patients in Italy multicenter trial will soon address this issue.

In concordance with the previously mentioned studies, 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, NIHSS >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 outcome but not for sICH increased with the number of concomitant 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 overestimated, 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 outcome and safety in patients given off-label thrombolysis.

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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