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Intravenous thrombolysis for acute ischaemic stroke in patients not fully adhering to the European licence in Poland

Leczenie trombolityczne udaru mózgu poza europejską rejestracją dla alteplazy w Polsce

Michał Karliński[1], Adam Kobayashi[1,2], Tomasz Litwin[1], Piotr Sobolewski[3], Waldemar Fryze[4], Sławomir Romanowicz[5], Michał Glonek[6], Walenty Nyka[7], Paweł Lisewski[8], Anna Członkowska[1,9]; on behalf of the SITS Poland Collaborative Group

[1]II Klinika Neurologiczna, Instytut Psychiatrii i Neurologii w Warszawie
[2]Centrum Interwencyjnego Leczenia Udaru Mózgu, Instytut Psychiatrii i Neurologii w Warszawie
[3]Oddział Neurologii, SP ZZOZ w Sandomierzu
[4]Oddział Neurologiczny, Pomorskie Centrum Traumatologii w Gdańsku
[5]Neurologia A, Wojewódzki Zespół Neuropsychiatryczny w Opolu
[6]Neurologia B, Wojewódzki Zespół Neuropsychiatryczny w Opolu
[7]Klinika Neurologii Dorosłych, Uniwersyteckie Centrum Kliniczne w Gdańsku
[8]Oddział Neurologii, Szpital Uniwersytecki nr 2 w Bydgoszczy
[9]Katedra i Zakład Farmakologii Doświadczalnej i Klinicznej, Warszawski Uniwersytet Medyczny

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Abstract

Background and purpose: The European licence for alteplase excludes from thrombolysis large groups of acute stroke patients. The Polish licence was revised in 2010, but until then many patients could receive the treatment only off-label. Our aim was to evaluate the safety and effectiveness of intravenous alteplase in Polish patients not fully adhering to the original European drug licence compared to patients treated strictly on-label.

Material and methods: We analysed all patient data contributed to the Safe Implementation of Thrombolysis in Stroke registry from Polish centres between October 2003 and July 2009.

Results: Off-label thrombolysis was administered in 224/946 (23.7%) patients. The most frequent deviations were: use of intravenous antihypertensives (8.2%), age > 80 years (5.4%), time-to-treatment > 3 hours (4.5%), oral anticoagulation (4.2%), previous stroke with concomitant diabetes (2.1%), and previous stroke ≤ 3 months (1.5%). We found no differences in the ratio of symptomatic intracranial haemorrhage

Streszczenie

Wstęp i cel pracy: Dostępność leczenia trombolitycznego w udarze niedokrwiennym mózgu jest ograniczona przez liczne przeciwwskazania zapisane w europejskiej rejestracji alteplazy. Polska charakterystyka produktu została uaktualniona w 2010 r., co znacząco rozszerzyło możliwości oficjalnego stosowania trombolizy. Celem badania była ocena bezpieczeństwa i skuteczności alteplazy podawanej dożylnie w udarze mózgu poza oficjalnymi wskazaniami lub przeciwwskazaniami w porównaniu z leczeniem w pełnej zgodności z europejską rejestracją.

Materiał i metody: Analizie poddano wszystkie przypadki leczenia trombolitycznego w Polsce zgłoszone do rejestru *Safe Implementation of Thrombolysis in Stroke* od października 2003 r. do lipca 2009 r.

Wyniki: Leczenie trombolityczne poza wskazaniami lub przeciwwskazaniami rejestracyjnymi przeprowadzono u 224/946 (23,7%) chorych. Najczęstszymi odstępstwami były: stosowanie dożylnych leków przeciwnadciśnieniowych (8,2%), wiek powyżej 80 lat (5,4%), czas od zachorowania do lecze-

Correspondence address: Michał Karliński, II Klinika Neurologiczna, Instytut Psychiatrii i Neurologii, ul. Sobieskiego 9, 02-957 Warszawa, e-mail: mkarlinski@ipin.edu.pl
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(sICH) according to SITS, ECASS and NINDS definitions. Adjusted odds for 3-month mortality were similar (OR 0.86, 95% CI: 0.51-2.41), excluding patients with previous stroke ≤ 3 months (OR 3.48, 95% CI: 0.96-12.7). Adjusted odds for death or dependency were slightly increased (OR 1.40, 95% CI: 0.92-2.13), especially in patients aged > 80 years (OR 2.80, 95% CI: 1.11-7.05), and with previous stroke ≤ 3 months (OR 4.07, 95% CI: 0.97-17.1).

Conclusions: Polish stroke patients receiving off-label thrombolysis tended to achieve a less favourable outcome, but they were not at increased risk of sICH or death. Considering the current Polish license for alteplase, it may be reasonable to additionally stratify the risk in patients aged > 80 years or with previous stroke ≤ 3 months.

Key words: acute stroke, thrombolysis, alteplase, off-label use, protocol, outcome.

nia > 3 godz. (4,5%), stosowanie doustnych antykoagulantów (4,2%), przebyty udar ze współistniejącą cukrzycą (2,1%), przebyty udar ≤ 3 miesięcy (1,5%). U pacjentów leczonych poza wskazaniami lub przeciwwskazaniami nie wykazano zwiększonej częstości występowania objawowego krwawienia wewnątrzczaszkowego (sICH) wg definicji SITS, ECASS i NINDS. Ryzyko zgonu w ciągu 3 miesięcy było porównywalne (OR 0,86; 95% CI: 0,51–2,41), z wyłączeniem podgrupy z przebytym udarem ≤ 3 miesięcy (OR 3,48; 95% CI: 0,96–12,7). Ryzyko zgonu lub niesprawności było nieznacznie zwiększone (OR 1,40; 95% CI: 0,92–2,13), zwłaszcza u chorych powyżej 80. roku życia (OR 2,80; 95% CI: 1,11–7,05) i po przebytym udarze mózgu ≤ 3 miesięcy (OR 4,07; 95% CI: 0,97–17,1).

Wnioski: Polscy pacjenci otrzymujący leczenie trombolityczne w udarze mózgu poza wskazaniami lub przeciwwskazaniami zapisanymi w europejskiej charakterystyce alteplazy uzyskują mniej korzystny efekt leczenia. Natomiast ryzyko sICH i zgonu jest porównywalne. W kontekście aktualnie obowiązujących zapisów rejestracyjnych zasadne wydaje się zindywidualizowane kwalifikowanie do leczenia chorych powyżej 80. roku życia lub z wywiadem udaru ≤ 3 miesięcy.

Słowa kluczowe: udar mózgu, leczenie trombolityczne, alteplaza, protokół, rokowanie.

Introduction

Recombinant tissue plasminogen activator (rt-PA, alteplase) is currently the only agent approved for thrombolytic therapy in acute ischaemic stroke [1-3]. Its safety and efficacy within 3 hours from stroke onset have been proved in randomized controlled clinical trials and confirmed by subsequent observational studies [4,5]. Unfortunately, the treatment is currently administered to approximately 5% of all ischaemic stroke patients, and up to 20% in thrombolysis-oriented centres [6,7]. Such a low proportion is probably due to organizational issues combined with numerous contraindications listed in the European drug licence [8]. The Polish licence for alteplase was revised in July 2010 according to the findings of the ECASS-3 trial [9]. However, until this recent amendment many patients (e.g. > 80 years of age, with time to treatment between 3 and 4.5 hours or requiring intravenous antihypertensives to maintain blood pressure < 185/110 mm Hg) could receive thrombolysis only off-label. The treatment was administered at the physician's discretion according to his individual judgment and published evidence [7,10,11]. Of note, in other European countries the original licence is still legally binding.

Treatment between 3 and 4.5 hours from the onset of symptoms has already been proved safe and effective [12,13]. There is also a growing body of evidence supporting thrombolysis in the elderly [14-17]. Nonetheless, still little is known about treatment outcome in other groups of patients not fully adhering to the European drug licence. Besides, the management of pre-existing comorbidities and stroke care in Poland is not as effective as in Western countries [18]. Therefore, a direct analysis of the national population is far more accurate than the estimates extrapolated from multinational studies, especially those conducted in Western Europe and the USA.

Our aim was to evaluate the safety and effectiveness of intravenous rt-PA in ischaemic stroke patients treated outside the European drug licence in Poland in comparison to patients treated strictly on-label.

Material and methods

The original European licence for alteplase in acute ischaemic stroke was conditionally approved by the European Medicines Agency (EMEA) in 2002. The licence required an EU-based multicentre, multina-

tional, academic driven, observational monitoring study to confirm the safety and effectiveness of thrombolysis in clinical practice [8]. As a consequence the Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST) was launched. It was based on the SITS International Registry of Thrombolysis in Stroke (SITS-ISTR) platform. SITS-MOST addressed only the European Union member countries by 2003, but cases of thrombolysis have been voluntarily reported to the SITS-ISTR by many Central and Eastern European stroke centres. SITS-MOST concluded in 2006, but the registry has been continuously expanding and presently is the largest source of information about thrombolysis. Our study is based on all patient data contributed by 28 Polish stroke centres between October 2003 and July 2009. In this period the Polish licence for alteplase was equivalent to the original European licence. The methodology of the SITS registry has been described in detail elsewhere [5]. The registry in Poland has been approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Data were acquired with the approval of the SITS-EAST Steering Committee and the international coordinator, checked for internal validity and processed for statistical analysis.

The off-label group consisted of patients fulfilling at least one of the following: age > 80 years, time-to-treatment > 3 h, use of oral anticoagulants, previous stroke within 3 months, a history of previous stroke and concomitant diabetes, use of unfractionated heparins (UFH), use of intravenous antihypertensives before thrombolysis, systolic blood pressure (SBP) > 185 mm Hg or diastolic blood pressure (DBP) > 110 mm Hg despite antihypertensive treatment, stroke severity > 25 points on the National Institute of Health Stroke Scale (NIHSS), blood glucose concentration < 2.8 or > 22.2 mmol/L.

Our outcome measures were 3-month mortality, combined death or dependency (modified Rankin Scale score [mRS] 3-6), and symptomatic intracranial haemorrhage (sICH).

We distinguished between sICH definitions according to SITS (i.e. local or remote parenchymal haematoma type 2 combined with NIHSS score worsening ≥ 4 points or death within 22-36 h [22]), European Cooperative Acute Stroke Study (ECASS) (i.e. any haemorrhage combined with NIHSS score worsening ≥ 4 points or death within 7 days [19]) and National Institute of Neurological Disorders and Stroke study (NINDS) (i.e. any haemorrhage combined with NIHSS score worsening ≥ 1 or death within 7 days [4]).

Statistical analysis

Categorical variables are presented as a ratio with the number of valid observations. Proportions were calculated with exclusion of unknown values from the denominator. Comparative analyses were planned for the off-label patients as a whole and in subgroups. In basic comparative statistics we used chi square test, with Yates' correction if the expected value was < 5. Continuous variables due to non-normal distribution are presented as median with interquartile range (IQR), and compared using Mann-Whitney U test. Odds are presented as a ratio (OR) with 95% confidence interval (95% CI).

The main analysis of particular licence deviations included all patients, also those with multiple deviations. In the sensitivity analysis we included only patients with isolated deviations, but calculations were not always mathematically possible due to the limited number of observations. We also did a separate analysis for patients with pooled less frequent deviations (i.e. previous stroke and diabetes, previous stroke ≤ 3 months, INR > 1.7, blood pressure > 185/110 mm Hg, NIHSS score > 25, blood glucose > 22.2 mmol/L). As the reference, we always used patients fully adhering to the European license.

To avoid variable selection caused by spurious correlations, only variables showing a relationship with the outcome in the univariate model (defined as $p < 0.10$) were included as potential predictors for constructing multivariate models. The final multivariate model for each outcome was identified using an interactive backward stepwise approach and included only independent ($p < 0.05$) outcome predictors. It was subsequently used to verify the influence of particular variables.

All tests were two-sided, and $p < 0.05$ was considered statistically significant. Calculations were carried out in STATISTICA 9.0 (StatSoft, Inc. 2010).

Results

A total of 960 patients were entered into the SITS registry by 28 Polish centres. We excluded 14 cases due to missing values in the critical variables. The final study population consisted of 946 patients (43.0% females), with median age 69 years (IQR: 59-76), and median onset-to-treatment time of 150 min (IQR: 125-170). Stroke severity on admission was mild (NIHSS score ≤ 7) in 25.8%, moderate (NIHSS score 8-14) in 37.2%, and severe (NIHSS score > 14) in 37.0% of cases.

Table 1. Deviations from the European license between 2003 and 2009

Particular deviations	N	Value
Intravenous antihypertensives	942	77 (8.2%)
Age >80 years	945	51 (5.4%)
Time to treatment > 3 h	946	43 (4.5%)
Time to treatment > 4.5 h	946	7 (0.7%)
Oral anticoagulants	943	40 (4.2%)
INR > 1.7	943	11 (1.2%)
Diabetes and previous stroke	931	20 (2.1%)
Previous stroke ≤ 3 months	942	14 (1.5%)
Treatment with UFH	943	5 (0.5%)
DBP > 110 mm Hg	916	4 (0.4%)
SBP > 185 mm Hg	916	3 (0.3%)
NIHSS score > 25 pts	922	2 (0.2%)
Glucose > 22.2 mmol/L*	902	1 (0.1%)

UFH – unfractionated heparin, DBP – diastolic blood pressure, SBP – systolic blood pressure, NIHSS – National Institutes of Health Stroke Scale

Data are presented as number of valid observations with ratio.

** There were no patients with glucose concentration < 2.8 mmol/L.*

Median NIHSS score was 12 (IQR: 7-17). Overall 3-month mortality reached 19.1%, while excellent (mRS 0-1) and favourable (mRS 0-2) outcomes were observed in 36.0% and 53.3% of cases, respectively.

Thrombolytic treatment with full adherence to the licence was administered in 681 (72.0%) patients. We identified 224 (23.7%) patients with at least one deviation, including 30 cases with double, and 2 cases with triple deviations. Due to missing data on licence adherence we were not able to clearly classify the remaining 41 (4.3%) patients. Academic centres tended to administer off-label thrombolysis more frequently than regular neurological wards (116/420 vs. 108/485, $p = 0.063$).

The most frequent deviations were: use of intravenous antihypertensives before rt-PA (8.2%), age > 80 years (5.4%), onset-to-treatment time > 3 h (4.5%), use of oral anticoagulants (4.2%), including cases with INR > 1.7 (1.2%), a history of previous stroke and concomitant diabetes (2.1%), and a history of previous stroke ≤ 3 months (1.5%). Other deviations were less frequent (Table 1).

Patients from the off-label group were significantly older, had a higher proportion of all stroke relevant comorbidities and pre-stroke disability, with longer onset-to-treatment time. However, we did not observe significant differences in stroke severity. Detailed comparative characteristics are shown in Table 2.

Both groups had a similar ratio of sICH according to SITS (1.9% vs. 1.4%), ECASS (6.7% vs. 5.4%), and NINDS (10.6% vs. 8.7%) definitions (Table 2). Multivariate analyses adjusted for independent outcome predictors also did not show increased odds for sICH in the off-label patients (Fig. 1).

There were no differences in 3-month mortality (21.8% vs. 18.6%) and favourable outcome (49.4% vs. 53.6%), but the off-label patients significantly less frequently achieved excellent outcome (29.2% vs. 37.6%, $p = 0.041$) (Table 2). Detailed distribution of mRS scores at 3 months is presented in Fig. 2.

We did not find a significant association between off-label thrombolysis and the risk of death at 3 months (OR 0.86, 95% CI: 0.51-2.41). Considering particular deviations, we observed a trend for higher mortality in patients with a history of previous stroke ≤ 3 months (OR 3.48, 95% CI: 0.96-12.7) (Fig. 3), but it was not confirmed in the sensitivity analysis (OR 2.52, 95% CI: 0.60-11.2, $p = 0.222$). All analyses were adjusted for the independent predictors (i.e. pre-stroke mRS of 0-1, diabetes, atrial fibrillation, congestive heart failure, oral antihypertensive treatment and NIHSS score at baseline).

We also did not find a significant association between off-label treatment and the combined risk of death and dependency (OR 1.40, 95% CI: 0.92-2.13). The negative trend was more marked in the subgroup with the less frequent deviations (OR 1.86, 95% CI: 0.92-3.79). Considering particular deviations, we observed increased odds for death or dependency in patients aged > 80 years (OR 2.80, 95% CI: 1.11-7.05), and a trend in patients with a history of previous stroke ≤ 3 months (OR 4.07, 95% CI: 0.97-17.1) (Fig. 4). In the sensitivity analysis those results did not reach significance (OR 2.57, 95% CI: 0.87-7.60, $p = 0.087$ and OR 3.72, 95% CI: 0.82-16.8, $p = 0.087$, respectively). All analyses were adjusted for independent predictors (i.e. pre-stroke mRS of 0-1, NIHSS score and glucose concentration at baseline).

Discussion

This is the first multicenter national study directly addressing the issue of off-label thrombolysis. Thanks to the recent amendment in the Polish drug licence for alteplase, onset-to-treatment time 3-4.5 h, age > 80 years and intravenous antihypertensive treatment are no long-

Table 2. Baseline characteristics and 3-month outcomes according to the licence adherence

	Off-label group		On-label group		*p-value*
	n	value	*n*	value	
Age (years)	223	73 (62-79)	681	68 (59-75)	< 0.001
Male gender	224	129 (57.6%)	681	382 (56.1%)	0.695
Body weight (kg)	223	76 (70-87)	678	77 (70-86)	0.528
Hypertension	221	181 (81.9%)	670	460 (68.6%)	< 0.001
Diabetes	224	46 (20.5%)	671	99 (14.8%)	0.042
Hyperlipidaemia	200	83 (41.5%)	622	204 (32.8%)	0.025
Atrial fibrillation	222	85 (38.3%)	671	194 (28.95)	0.009
Congestive heart failure	222	53 (23.9%)	665	114 (17.1%)	0.026
Prior stroke	222	55 (24.8%)	681	53 (7.8%)	< 0.001
Smoking status					
current smoker	214	51 (23.8%)	656	180 (27.4%)	0.299
never smoker	209	127 (60.8%)	626	357 (57.0%)	0.343
Pre-stroke aspirin use	220	69 (31.4%)	675	194 (28.7%)	0.458
Pre-stroke LMWH	223	7 (3.1%)	681	21 (3.1%)	0.967
Antihypertensive treatment					
any medication	220	165 (75.0%)	678	278 (41.0%)	< 0.001
oral medication	220	126 (57.3%)	678	278 (41.0%)	< 0.001
intravenous medication	224	77 (34.4%)	681	0 (0.0%)	< 0.001
Pre-stroke functional status (mRS)	219	0 (0-1)	672	0 (0-0)	< 0.001
excellent (mRS ≤ 1)	219	188 (85.8%)	672	632 (94.1%)	< 0.001
Stroke severity (NIHSS)	208	11 (7-17)	681	12 (8-17)	0.324
mild (NIHSS ≤ 7)	208	65 (31.3%)	681	162 (23.8%)	0.031
moderate (NIHSS 8-14)	208	69 (33.2%)	681	264 (38.8%)	0.145
severe (NIHSS ≥ 15)	208	74 (35.6%)	681	255 (37.4%)	0.625
CT imaging before thrombolysis					
hyperdense artery sign	204	23 (11.3%)	665	77 (11.6%)	0.905
current infarct	204	29 (14.2%)	665	123 (18.5%)	0.159
Systolic BP (mm Hg)	211	160 (144-170)	681	148 (134-160)	< 0.001
Diastolic BP (mm Hg)	211	90 (80-100)	681	83 (79-90)	< 0.001
Blood glucose concentration (mmol/L)	202	6.5 (5.8-7.7)	681	6.6 (5.7-7.9)	0.928
Onset-to-treatment time (min)	222	160 (130-180)	679	150 (120-170)	< 0.001
time to treatment < 90 min	222	15 (6.8%)	679	51 (7.5%)	0.708
Symptomatic intracranial haemorrhage					
according to SITS	208	4 (1.9%)	666	9 (1.4%)	0.790*
according to ECASS	208	14 (6.7%)	666	36 (5.4%)	0.472
according to NINDS	208	22 (10.6%)	666	58 (8.7%)	0.415

Table 2. cont.

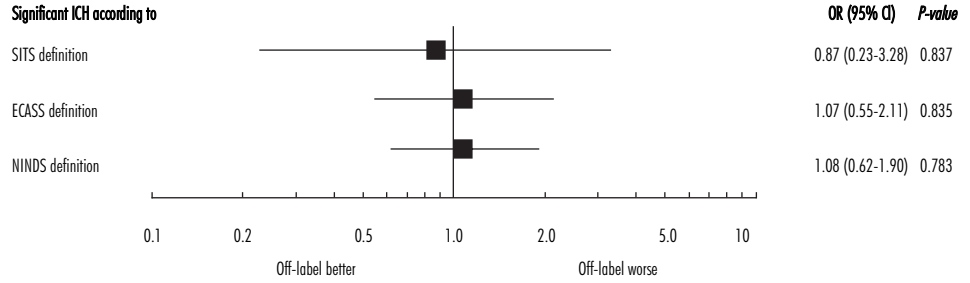
	Off-label group		On-label group		p
	n	value	n	value	
Death at 3 months	179	39 (21.8%)	571	106 (18.6%)	0.341
Functional outcome at 3 months					
excellent (mRS 0-1)	178	52 (29.2%)	569	214 (37.6%)	0.041
favourable (mRS 0-2)	178	88 (49.4%)	569	305 (53.6%)	0.331

LMWH – low-molecular-weight heparin, mRS – modified Rankin Scale, BP – blood pressure, NIHSS – National Institutes of Health Stroke Scale, CT – computed tomography, SITS – Safe Implementation of Thrombolysis in Stroke, ECASS – European Cooperative Acute Stroke Study, NINDS – National Institute of Neurological Disorders and Stroke

Data are presented as median (IQR) or number (%).

P-value for categorical variables was calculated with χ^2 test and Mann-Whitney U-test for continuous variables.

** Yates' correction was applied.*



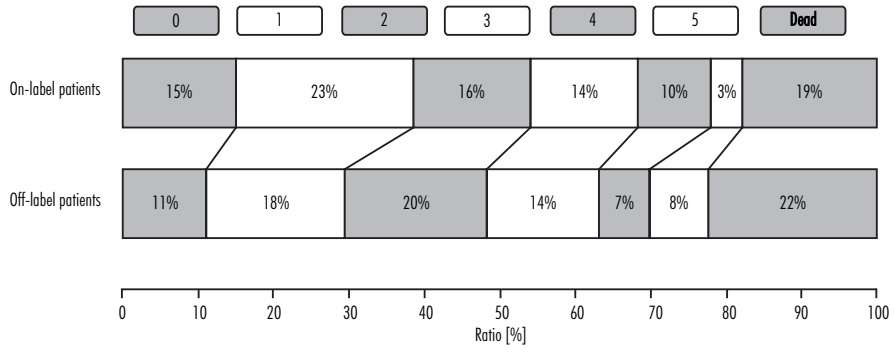
** Adjusted for oral antihypertensive treatment*

*** Adjusted for atrial fibrillation, stroke severity and oral antihypertensive treatment*

**** Adjusted for atrial fibrillation, diabetes, stroke severity, oral antihypertensive treatment and current infarct on CT imaging before thrombolysis*

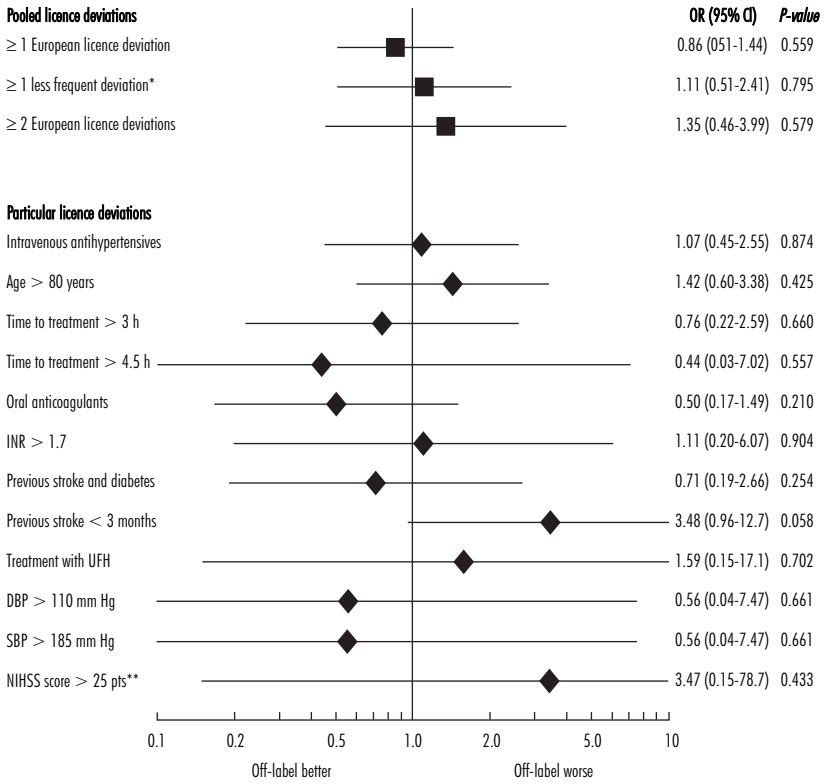
SITS – Safe Implementation of Thrombolysis in Stroke, ECASS – European Cooperative Acute Stroke Study, NINDS – National Institute of Neurological Disorders and Stroke

Fig. 1. Odds ratio (OR) for symptomatic intracranial haemorrhage (ICH) adjusted for independent predictors



Ratio of patients achieving excellent score (mRS 0-1) was significantly ($p < 0.05$) lower in the off-label group

Fig. 2. Distribution of modified Rankin scale (mRS) scores at 3 months



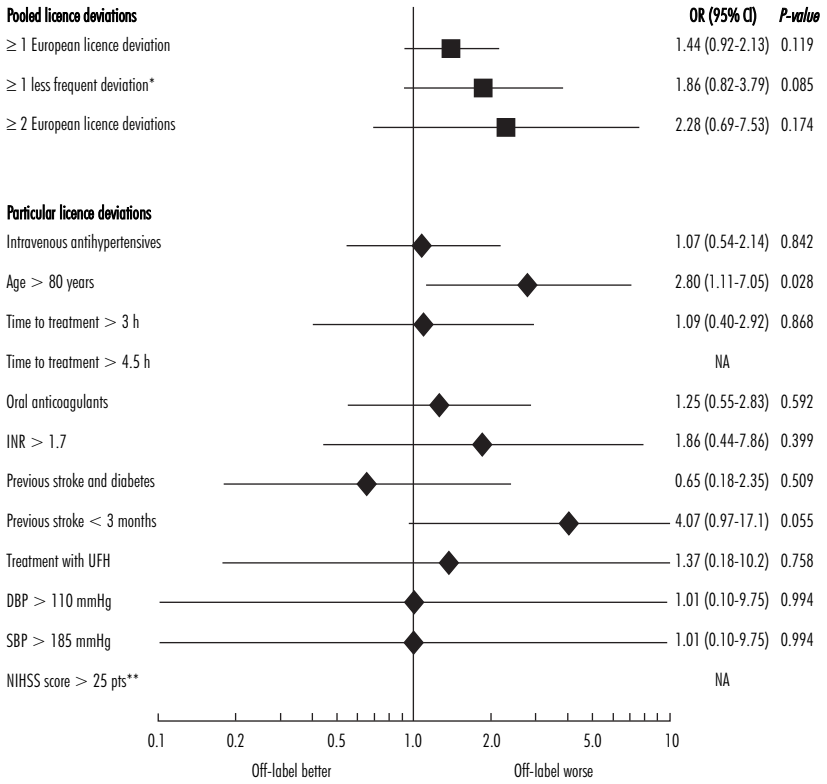
** Previous stroke and diabetes, previous stroke ≤ 3 months, INR > 1.7, blood pressure > 185/110 mm Hg, NIHSS score > 25, blood glucose > 22.2 mmol/L.*
*** Model excluding baseline NIHSS score as a covariate.*
NIHSS – National Institutes of Health Stroke Scale, UFH – unfractionated heparin, DBP – diastolic blood pressure, SBP – systolic blood pressure

Fig. 3. Odds ratio (OR) for 3-month mortality adjusted for independent predictors (i.e. pre-stroke modified Rankin scale score 0-1, diabetes, atrial fibrillation, congestive heart failure, stroke severity and oral antihypertensive treatment)

er formal contraindications. However, other contraindications are still binding and the European licence has not been updated yet. Besides, even the new Polish licence recommends individual assessment of the risk/benefit ratio in the elderly [9]. As we mentioned before, health care systems in different countries are not equivalent. In this respect, our findings should facilitate decision making in clinical practice, particularly in Poland and countries of Central and Eastern Europe. The study also gives feedback to Polish stroke centres, which despite growing experience in thrombolysis still have much room for improvement.

According to our data, patients not adhering to the European license did not have an increased risk of sICH and 3-month mortality. They tended to achieve a worse functional outcome, especially patients > 80 years of age. We also found a marked trend for increased risk of death and death or dependency in patients with previous stroke < 3 months.

In a multinational analysis including 5594 patients entered in the SITS registry by 9 Central and Eastern Countries, 34.3% of patients received thrombolysis off-label. There was a higher ratio of patients treated >3 h (13.1%), but other deviations occurred with a similar frequency. The off-label patients had a significantly higher ratio of sICH according to the ECASS definition (7.1% vs. 5.3%), not confirmed in the multivariate model. They also tended to have increased risk of death at 3 months (OR 1.17, 95% CI: 0.97-1.42), especially in patients > 80 years of age (OR 1.41, 95% CI: 0.92-2.18). The risk of death or dependency was significantly increased (OR 1.26, 95% CI: 1.08-1.48). The methodology of that study was very similar, but because of the large number of included patients it was possible to calculate multivariate odds for particular deviations using only patients with isolated deviations [20]. Those results partially concur with our findings. However, we observed a negative trend for patients with previous



** Previous stroke and diabetes, previous stroke ≤ 3 months, INR > 1.7, blood pressure > 185/110 mm Hg, NIHSS score > 25, blood glucose > 22.2 mmol/L*
*** Model excluding baseline NIHSS score as a covariate*
NIHSS – National Institutes of Health Stroke Scale, UFH – unfractionated heparin, DBP – diastolic blood pressure, SBP – systolic blood pressure

Fig. 4. Odds ratio (OR) for death or dependency (modified Rankin scale [mRS] 3-6) adjusted for independent predictors (i.e. pre-stroke mRS 0-1, stroke severity and glucose concentration at baseline)

stroke ≤ 3 months, and the age > 80 years affected mortality rather than functional outcome. It may be in some way specific to the Polish population.

Safety and effectiveness of thrombolysis outside the European licence has also been assessed by Meretoja *et al.* In their study, off-label alteplase was administered to 499/985 consecutive patients admitted to a single centre in Helsinki. The most frequent deviations were age > 80 years (16%), mild stroke (13%), use of intravenous antihypertensives (11%), onset-to-treatment time > 3 h (10%), blood pressure > 185/110 mm Hg (5%) and oral anticoagulation (4%). The risk of sICH according to the ECASS definition was not increased in the off-label patients (OR 0.80, 95% CI: 0.43-1.48). However, they tended to have increased odds for death or dependency (OR 1.37, 95% CI: 0.95-1.97), which was significant in the subgroup aged > 80 years. The study by Meretoja *et al.* did not examine mortality, excluded patients with basilar artery occlusion, and considered baseline NIHSS 0-4 a license deviation. Its multivariate model included 21 variables and was not limited to independent outcome predictors. Besides, the logistics in Helsinki was significantly better (i.e. 34 min median door-to-treatment time), and a more favourable overall outcome was noted (8.7% on-label mortality) [21]. Despite those methodological differences, the results are consistent with ours.

A study by Rubiera *et al.* assessed adherence to the SITS-MOST protocol in 369 non-lacunar stroke patients with a documented intracranial artery occlusion, INR < 1.8 and mismatch on multiparametric MRI if treated 3 to 6 hours from the onset of symptoms. The non-protocol group consisted of patients treated within 3-6 hours from onset, aged > 80 years, with stroke severity > 25 in NIHSS, and a history of previous stroke and concomitant diabetes. There were no differences in the rate of sICH. However, the non-protocol group showed a trend for increased 3-month

mortality (16.1% vs. 10.5%; $p = 0.084$) and a higher ratio of death or dependency (60.4% vs. 51.7%; $p = 0.082$). After excluding patients > 80 years of age, the proportion of unfavourable outcome was comparable to the per-protocol group [11]. Despite certain methodological differences (i.e. narrow inclusion criteria, median NIHSS score of 17, and 124 thrombolyses > 3 hours from onset of symptoms) these results are generally consistent with ours, especially in the group > 80 years of age.

All above-mentioned studies show that thrombolysis in patients not fully adhering to the SITS protocol (European licence) may be less beneficial in comparison to strict on-label treatment. However, it does not allow one to conclude that those patients do not benefit from thrombolysis. Such evidence can be reliably provided only by the ongoing randomized controlled clinical trials (e.g. Third International Stroke Trial [IST-3], Thrombolysis in Elderly Stroke Patients in Italy [TESPI]) [22,23]. Presently, the indirect controlled comparisons of treated versus untreated patients offer reassurance that intravenous thrombolysis is beneficial at least in some off-label patients (e.g. the elderly or those with concomitant diabetes and prior stroke) [17,24]. However, in other groups (i.e. NIHSS < 4 or > 25) it appears to be dubious [25].

To our best knowledge, there is no direct evidence against using intravenous antihypertensives to maintain blood pressure < 185/110 mm Hg before and during thrombolysis [26]. On the contrary, withholding antihypertensives in patients with a history of hypertension may result in worse outcome [27]. Effective management of blood pressure with easily reversible intravenous agents enables optimal control of very high blood pressure, and therefore should not be considered a contraindication for rt-PA. Our results support this thesis.

The evidence encourages thrombolysis in patients > 80 years of age, but it is still discussed if we should treat the elderly without any limits or maybe additionally stratify their risk/benefit ratio. A meta-analysis of cohort studies by Engelter *et al.* indicates that patients aged > 80 years had higher 3-month mortality and were less likely to achieve excellent outcome (mRS ≤ 1) [14]. In a more recent meta-analysis by Meseguer *et al.*, mortality was not assessed, but the likelihood of an unfavourable outcome was also increased [15]. Unfortunately, neither analysis adjusted for other outcome predictors. A recent study by Ford *et al.* shows that the elderly from the whole SITS-ISTR population had a higher 3-month mortality rate and reduced independence [16]. Importantly, the risk of sICH was not increased. This partially concurs with our findings showing that age > 80 years may have a negative effect on functional outcome.

Intravenous thrombolysis ≤ 4.5 hours from the onset of symptoms or even beyond this time window has already been proved safe and effective [12,13,19]. In our study, patients treated > 3 hours from the onset did not show an increased risk of worse outcome, which is more optimistic than in large multinational analyses [20,28]. We hypothesize that this difference may be due to a positively biased patient selection in Polish centres and a relatively small number of those patients ($n = 43$).

According to our findings, ineffective oral anticoagulation probably does not increase the risk of death or unfavourable outcome. Although concerns about sICH have been raised by Prabhakaran *et al.* [29], we think that available evidence should not discourage thrombolysis in patients with INR < 1.7.

The evidence on previous stroke and concomitant diabetes, as well as previous stroke ≤ 3 months, is limited [10,20,21,24] but it does not justify withholding treatment in those patients. In our study, patients with a history of previous stroke ≤ 3 months may achieve a worse outcome. This finding was slightly beyond significance and was not confirmed in the sensitivity analysis. However, the point estimates were high and it is possible that a larger sample would have yielded significant results. Therefore, we should be careful when administering thrombolysis to patients with a previous stroke ≤ 3 months, at least in the Polish setting.

In our material there were only two patients with an NIHSS score > 25 and one patient with blood glucose concentration > 22.2 mmol/L. Elevated blood glucose is associated with worse prognosis irrespectively of thrombolysis [20,30], and increases the odds for sICH after treatment [20,30,31]. Therefore, we need to be extremely cautious considering alteplase in patients with glucose concentration > 22.2 mmol/L. A similar statement can be made about NIHSS score > 25 [20,25].

Our study has limitations. It is based on a voluntary registry. Therefore, it is not possible to identify how many patients were not reported to the database and for what reasons. We may not exclude that some of them died early, had sICH or received rt-PA despite other severe licence deviations. Outcomes may also be biased because of the non-random sampling. On-label patients

are most likely consecutive, but the off-label patients were selected at the physician's discretion. To minimize the influence of confounders (e.g. worse comorbidity state in the off-label group) we used multivariate models adjusted for all independent outcome predictors. However, it does not eliminate their influence completely. We decided to include cases with isolated missing values to make particular estimates more precise, but even then the number of valid cases was often low. Therefore, the sensitivity analysis was not always possible and confidence intervals not narrow enough to draw strong conclusions.

Nonetheless, our findings show that in Poland, in one in four cases, thrombolysis for acute stroke was administered outside the drug license. The off-label patients achieved comparable or slightly worse outcome, but they were not at increased risk of sICH. Some contraindications appear definitely redundant (e.g. aggressive blood pressure management with intravenous medication, previous stroke with concomitant diabetes, oral anticoagulation with INR < 1.7). Our everyday clinical decision making should rely on evidence and guidelines. In Poland, the license for alteplase has recently become more guideline-adherent, but in some patients we still may have the dilemma of denying thrombolysis only because of licence limitations. It may be reasonable to use individual risk stratification in patients > 80 years of age or with a history of previous stroke ≤ 3 months. However, to make final conclusions in this matter we still need the results of ongoing randomized trials and other controlled studies.

Conclusions

1. One in four cases of intravenous thrombolysis for acute stroke in Poland was administered outside the European drug license.
2. The off-label patients achieved comparable or slightly worse outcome, but they were not at increased risk of sICH or death.
3. Some contraindications appear definitely redundant (e.g. aggressive blood pressure management with intravenous medication, previous stroke with concomitant diabetes, oral anticoagulation with INR < 1.7).
4. Our everyday clinical decision making should rely on evidence and guidelines. In Poland, the licence for alteplase has recently become more guideline-adherent, but in some patients we still may have the dilemma of denying thrombolysis only because of licence limitations.
5. It may be reasonable to use individual risk stratification in patients > 80 years of age or with a history of previous stroke ≤ 3 months. However, to make final conclusions in this matter we still need the results of ongoing randomized trials and other controlled studies.

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Disclosure

Authors report no conflict of interest.

Appendix

The following centres from the SITS Poland Collaborative Group contributed to this study (name of the hospital and local coordinator with the number of included patients):

II Klinika Neurologiczna IPiN w Warszawie (A. Kobayashi – 225), SP ZZOZ w Sandomierzu (P. Sobolewski – 120); Pomorskie Centrum Traumatologii w Gdańsku (W. Fryze – 75); Wojewódzki Zespół Neuropsychiatryczny w Opolu (S. Romanowicz – 74); Uniwersyteckie Centrum Kliniczne w Gdańsku (W. Nyka – 71); Szpital Uniwersytecki nr 2 w Bydgoszczy (P. Lisewski – 66); CSK MSWiA w Warszawie (M. Dorobek – 48); SP CSK SUM w Katowicach (G. Opala – 42); Szpital Wolski w Warszawie (A. Kuczyńska-Zardzewiały – 41); Szpital Specjalistyczny w Pile (M. Wiszniewska – 36); Szpital Specjalistyczny w Końskich (M. Fudala – 30); Szpital Powiatowy w Skarżysko-Kamiennej (J. Stoiński – 23); I Klinika Neurologiczna IPiN w Warszawie (P. Richter – 18); Szpital Wojewódzki w Poznaniu (J. Michalska – 13); Szpital Specjalistyczny w Kościerzynie (A. Walczak – 9); Szpital Specjalistyczny w Siedlcach (P. Kwiatkowski – 8); SP CSK WUM w Warszawie (H. Kwieciński – 7); WIM w Warszawie (J. Stępień – 7); Szpital Wojewódzki nr 2 w Rzeszowie (M. Zięba – 7); Wojewódzki Szpital Podkarpacki w Krośnie (R. Jucha – 6); Dolnośląski Szpital Specjalistyczny we Wrocławiu (K. Gurański – 5); Wojewódzki Szpital Specjalistyczny w Olsztynie (A. Tutaj – 5); SPPK CMKP w Warszawie (W. Palasik – 4); Uniwersytecki Szpital Kliniczny

w Białymstoku (W. Drozdowski – 3); Górnośląskie Centrum Medyczne w Katowicach (A. Warsz-Wianecka – 3).

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