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Is there a bad time for intravenous thrombolysis? The experience of Polish stroke centers

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ABSTRACT

Background and purpose: The outcome in acute stroke strongly depends on patient-related issues, as well as on the availability of human and diagnostic resources. Our aim was to evaluate safety and effectiveness of intravenous alteplase for stroke according to the time of admission to the hospital.

Materials and methods: We analyzed the data of all acute stroke patients treated with alteplase between October 2003 and December 2010, contributed to the Safe Implementation of Thrombolysis for Stroke registry from 27 Polish stroke centers. According to the time of admission we distinguished between: (1) non-working days (Friday 14:30–Monday 08:00 plus national holidays); (2) out-of-office hours (non-working days plus 14:30–08:00 during working days); and (3) night hours (time from 23:00 to 06:00). Patients admitted during regular working hours (Monday 08:00–Friday 14:30, excluding national holidays) were used as the reference.

Results: Of 1330 patients, 448 (32.5%) were admitted on non-working days, 868 (65.3%) at out-of-office hours, and 105 (7.9%) during night hours. In multivariate logistic regression, none of the evaluated periods showed association with symptomatic intracranial hemorrhage, 7-day mortality, and neurological improvement $\geq$4 points in the National Institutes of Health Stroke Scale score at day 7. Patients admitted during night hours had lower odds (OR 0.53, 95% CI: 0.29–0.95, $p = 0.032$) for achieving favorable outcome (modified Rankin Scale score 0–2).

Conclusions: There is no bad time for thrombolysis. Stroke centers should feel confident about the treatment outside regular working hours, irrespective of equipment and staff availability. However, it may be reasonable to pay additional attention during nighttime.

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1. Introduction

Treatment with recombinant tissue plasminogen activator (rtPA, alteplase) within the first 4.5 h from the onset of symptoms is currently the gold standard of stroke care in developed countries [1–3]. Its effectiveness and safety depend not only on patient-related issues, but also on human and diagnostic resources. As the availability of those resources is not equal 24 h a day and 7 days a week (24/7), the time of admission may affect both the quality of care and the final outcome [4,5].

Several studies have described the so-called 'weekend phenomenon' [5–12]. Some authors also suggest that patients admitted during out-of-office hours [13,14] or night hours [7,15,16] may achieve less favorable outcome. However, the amount of evidence is still not sufficient, especially regarding treatment with rtPA. In Poland, the weekend phenomenon has been previously addressed only in one study that included unselected ischemic stroke patients, and did not account for thrombolysis [12].

The aim of our study was to evaluate safety and effectiveness of intravenous rtPA for ischemic stroke depending on the time of admission to the hospital, including out-of-office hours, non-working days and night hours. Additional emphasis was put on the treatment logistics.

2. Materials and methods

We analyzed the data of all acute stroke patients treated with intravenous rtPA between October 2003 and December 2010 contributed to the Safe Implementation of Treatments in Stroke – Eastern Europe (SITS-EAST) registry by 27 Polish stroke centers.

SITS-EAST is an international study of implementation of evidence-based stroke therapy supported by the SITS International Registry of Thrombolysis in Stroke (SITS-ISTR). The details of the SITS methodology, rationale for SITS-EAST and Polish participation in the registry have been described in detail elsewhere [17–19]. Briefly, SITS was originally a European Union-based, multinational, academic-driven, monitoring study designed to confirm the safety and effectiveness of thrombolysis in clinical practice [20]. Despite achieving its original aim in 2006, the registry as a platform has been constantly expanding. Currently, it is the largest source of data about licensed thrombolysis for stroke.

The registry in Poland has been approved by the local Ethics Committee. Data for the present analysis were acquired in August 2011 with the approval of the National Coordinator (Prof. Anna Czlonkowska). To ensure completeness of the 3-month follow-up, we decided not to include patients treated in the year 2011.

According to the time of admission, we distinguished between: (1) non-working days – defined as Friday 14:30–Monday 08:00 plus national holidays; (2) out-of-office hours – defined as non-working days plus hours 14:30–08:00 during the working days; and (3) night hours – defined as the time from 23:00 to 06:00.

Our major endpoints were the following: (1) symptomatic intracranial hemorrhage (sICH) according to the ECASS II definition (i.e. any intracranial hemorrhage combined with National Institutes of Health Stroke Scale [NIHSS] score worsening of $\geq$4 points or leading to death within 7 days); (2) 7-day mortality; (3) significant neurological improvement (i.e. improvement of $\geq$4 points on the NIHSS or achieving the NIHSS score of 0); (4) favorable outcome at 3-month follow-up (i.e. modified Rankin Scale [mRS] score of 0–2 points, meaning alive and independent) [21]. The ECASS II definition of sICH was chosen because it allows to effectively predict the worst outcome after thrombolysis [22]. As the measures of treatment logistics, we used onset-to-treatment time (OTT), and door-to-needle time (DNT) with special emphasis on DNT $\leq$60 min.

2.1. Statistical analysis

Categorical variables are presented as a number of valid observations with ratio. Proportions were calculated with exclusion of unknown values from the denominator. Due to non-normal distribution, continuous variables are presented as a median with interquartile range (IQR, representing 50% of average observations surrounding the median).

All analyses were made using regular working hours (Monday 08:00–Friday 14:30, excluding national holidays) as a reference. For basic comparisons, we used χ^2 test (with Yates correction if the expected value in at least one cell of a 2×2 contingency table was $<$5) or Mann–Whitney *U*-test. To calculate odds ratios (OR) with 95% confidence interval (95% CI) for each primary endpoint, we used multivariable logistic regression. All regression models were arbitrarily adjusted for age, lack of prestroke disability (mRS score $\leq$1), baseline NIHSS score, and OTT $\leq$90 min.

Calculations were carried out in STATISTICA 10.0 (Stat Soft Inc., Tulsa, USA, 2011). We considered a p-value $<$0.05 statistically significant. In tables, p-values $>$0.100 are presented as non-significant (NS).

3. Results

In the study period, 1330 cases of intravenous thrombolysis were reported to the registry, including 868 (65.3%) patients admitted at out-of-office hours, 448 (32.5%) admitted on non-working days, and 105 (7.9%) admitted during night hours. The reference group consisted of 462 patients admitted during regular working hours (Fig. 1).

3.1. Out-of-office hours

Patients admitted at out-of-office hours did not differ from the patients admitted during working hours in terms of distribution of vascular risk factors, but more frequently presented with no preexisting disability (92.9% vs. 88.2%, $p = 0.004$). They had a significantly lower proportion of mild strokes (NIHSS score $\leq$7) and more frequently showed hyperdense artery sign on the pretreatment brain computed tomography (CT) (Table 1). We found no differences in the median OTT and DNT, but patients admitted at out-of-office hours less frequently received thrombolysis within the first 90 min from the onset of symptoms (7.3% vs. 12.1%, $p = 0.003$) (Table 1). The occurrence of sICH, neurological worsening and the

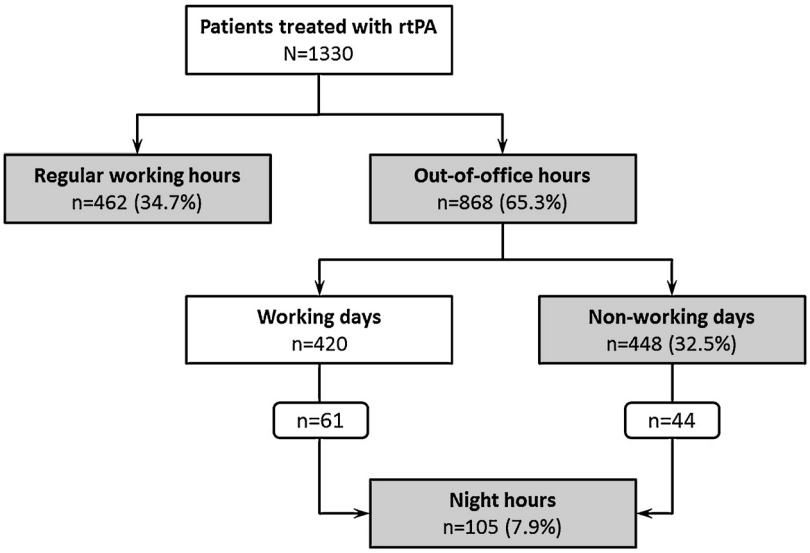

Fig. 1 – Groups of patients according to the time of admission. rtPA – recombinant tissue plasminogen activator.

distribution of the 3-month mRS scores were similar between the groups (Table 2; Fig. 2). In a multivariate analysis (adjusted for age, lack of prestroke disability, baseline NIHSS score and OTT ≤90 min), the admission out-of-office hours showed no association with major endpoints (Table 3).

3.2. *Non-working days*

Patients admitted on non-working days had a similar distribution of vascular risk factors compared to patients admitted during regular hours. They more frequently

Table 1 – Baseline characteristics using regular hours admissions as a reference.

	Regular hours		Out-of-office hours			Non-working days			Night hours		
	N	Value	N	Value	p	N	Value	p	N	Value	p
Age (years)	462	69 (60–76)	868	68 (59–76)	NS	448	69 (60–76)	NS	105	64 (54–72)	<0.001
Male gender	462	260 (56.3%)	868	494 (56.9%)	NS	448	258 (57.6%)	NS	105	67 (63.8%)	NS
Hypertension	456	331 (72.6%)	855	623 (72.9%)	NS	441	328 (74.4%)	NS	104	64 (61.5%)	0.026
Diabetes	459	80 (17.4%0	857	149 (17.4%)	NS	441	70 (15.9%)	NS	104	18 (17.3%)	NS
Hyperlipidaemia	412	152 (36.9%)	797	257 (32.3%)	NS	415	135 (32.5%)	NS	96	30 (31.3%)	NS
Atrial fibrillation	457	145 (31.7%)	853	264 (31.0%)	NS	440	135 (30.7%)	NS	103	33 (32.0%)	NS
Congestive heart failure	454	83 (18.3%)	851	158 (18.6%)	NS	439	84 (19.1%)	NS	103	16 (15.5%)	NS
Prior stroke	460	62 (13.5%)	864	106 (12.3%)	NS	444	60 (13.5%)	NS	105	8 (7.6%)	NS
Prestroke antiplatelet use	461	153 (33.2%)	864	263 (30.4%)	NS	446	143 (32.1%)	NS	105	32 (30.5%)	NS
No prestroke disability (mRS ≤1)	448	385 (88.2%)	835	776 (92.9%)	0.004	427	394 (92.3%)	0.042	99	93 (93.9%)	0.094
Stroke severity (NIHSS)	459	11 (7–17)	866	12 (8–16)	NS	447	12 (8–16)	NS	105	13 (8–16)	NS
- Mild (NIHSS ≤7)	459	129 (28.1%)	866	199 (23.0%)	0.040	447	102 (22.8%)	0.068	105	17 (16.2%)	0.012
- Moderate (NIHSS 8–14)	459	163 (35.5%)	866	350 (40.4%)	0.081	447	184 (41.2%)	0.080	105	42 (40.0%)	NS
- Severe (NIHSS ≥15)	459	167 (36.4%)	866	317 (36.6%)	NS	447	161 (36.0%)	NS	105	46 (43.8%)	NS
Hyperdense artery sign on CT	448	44 (9.8%)	842	120 (14.3%)	0.023	435	57 (13.1%)	NS	104	16 (15.4%)	NS
Systolic blood pressure (mm Hg)	459	150 (138–165)	863	150 (140–165)	NS	447	150 (137–166)	NS	103	150 (130–160)	NS
Diastolic blood pressure (mm Hg)	459	85 (80–90)	863	85 (80–93)	NS	447	85 (80–90)	NS	103	80 (75–92)	NS
Intravenous antihyper-tensives	445	33 (7.4%)	836	59 (7.1%)	NS	430	33 (7.7%)	NS	102	4 (3.9%)	NS
Blood glucose (mg/dL)	443	120 (103–149)	843	121 (107–142)	NS	431	122 (108–145)	NS	101	123 (114–136)	NS

Data are presented as number of observations (ratio) or median (interquartile range).
mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale, CT – computed tomography.

Table 2 – Treatment logistics and outcome using regular hours admissions as a reference.

	Regular hours		Out-of-office hours			Non-working days			Night hours		
	N	Value	N	Value	p	N	Value	p	N	Value	p
Onset-to-treatment time (min)	462	150 (120–170)	867	150 (120–170)	NS	448	148 (120–165)	NS	105	150 (120–170)	NS
- 90 min or less	462	56 (12.1%)	867	63 (7.3%)	0.003	448	30 (6.7%)	0.005	105	8 (7.6%)	NS
Door-to-needle time (min)	462	75 (54–103)	867	72 (55–97)	NS	448	70 (53–95)	NS	105	76 (59–90)	NS
- 60 min or less	462	160 (34.6%)	867	300 (34.6%)	NS	448	167 (37.3%)	NS	105	32 (30.5%)	NS
sICH according to ECASS II def.	455	24 (5.3%)	847	39 (4.6%)	NS	443	26 (5.9%)	NS	105	3 (2.9%)	NS
Outcome at day 7											
- Improvement ≥4 on NIHSS	445	279 (62.7%)	837	481 (57.5%)	NS	435	243 (55.9%)	0.039	98	56 (57.1%)	NS
- Worsening ≥4 on NIHSS	445	53 (11.9%)	837	104 (12.4%)	NS	435	61 (14.0%)	NS	98	12 (12.2%)	NS
- Death	458	34 (7.4%)	837	66 (7.7%)	NS	446	41 (9.2%)	NS	103	7 (6.8%)	NS
Outcome after 3 months											
- Excellent (mRS 0–1)	353	124 (35.1%)	683	244 (35.7%)	NS	363	128 (35.3%)	NS	76	22 (29.0%)	NS
- Favorable (mRS 0–2)	353	188 (53.3%)	683	357 (52.3%)	NS	363	184 (50.7%)	NS	76	32 (42.1%)	0.078
Death	355	63 (17.8%)	685	132 (19.3%)	NS	364	74 (20.3%)	NS	76	14 (18.4%)	NS

Data are presented as number of observations (ratio) or median (interquartile range), sICH – symptomatic intracranial hemorrhage. mRS – modified Rankin Scale, ECASS II – the European Cooperative Acute Stroke Study II, NIHSS – National Institutes of Health Stroke Scale.

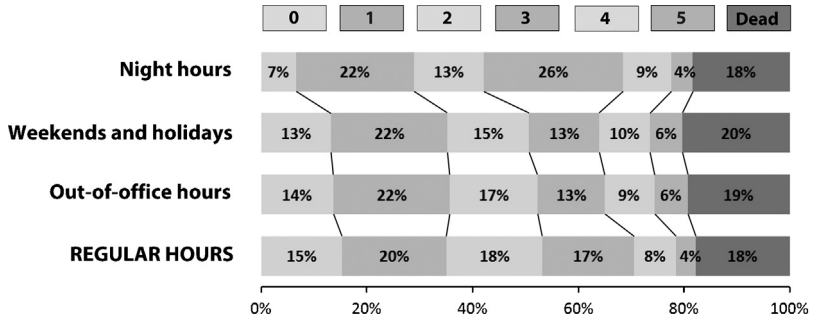

Fig. 2 – The distribution of modified Rankin Scale (mRS) scores at the 3-month follow-up according to the time of admission.

Table 3 – Odds ratios (OR) for the primary endpoints calculated using multivariate logistic regression.

	sICH according to ECASS		Death at 7 days		Significant improvement		Favorable outcome	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Evaluated variables[a]								
- Out-of-office hours	0.86 (0.50–1.49)	NS	1.08 (0.68–1.71)	NS	0.82 (0.65–1.05)	NS	0.90 (0.67–1.22)	NS
- Non-working days	1.15 (0.64–2.07)	NS	1.30 (0.77–2.17)	NS	0.80 (0.61–1.06)	NS	0.85 (0.60–1.20)	NS
- Night hours	0.71 (0.21–2.48)	NS	1.02 (0.41–2.52)	NS	0.72 (0.45–1.14)	NS	0.53 (0.29–0.95)	0.032
Covariables								
- No prestroke disability (mRS ≤1)	0.46 (0.23–0.93)	0.030	1.08 (0.53–2.20)	NS	1.05 (0.69–1.59)	NS	2.2 (1.3–3.8)	0.001
- Age (for each 5 years)	1.11 (0.91–1.26)	NS	1.07 (0.96–1.19)	NS	0.98 (0.93–1.03)	NS	0.93 (0.86–0.99)	0.027
- Baseline NIHSS (for each 4 points)	1.29 (1.07–1.55)	0.007	1.75 (1.48–2.06)	<0.001	0.94 (0.86–1.02)	NS	0.46 (0.41–0.51)	<0.001
- Time to treatment ≤90 min	0.81 (0.31–2.10)	NS	1.19 (0.59–2.43)	NS	1.02 (0.68–1.51)	NS	1.2 (0.7–1.92)	NS

[a] Each multivariate model included one of the evaluated variables and was adjusted for all four covariables.
CI – confidence interval, ECASS – the European Cooperative Acute Stroke Study, mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale, sICH – symptomatic intracranial hemorrhage.

presented with no preexisting disability (92.3% vs. 88.2%, $p = 0.042$) and tended to have a lower proportion of mild strokes (Table 1). Despite similar median OTT, they were less frequently treated within the first 90 min from the onset of symptoms (6.7% vs. 12.1%, $p = 0.003$). There were no differences in the occurrence of sICH, neurological worsening and the distribution of the 3-month mRS scores (Table 2; Fig. 2). Patients admitted on non-working days less frequently achieved neurological improvement (55.9% vs. 62.7%, $p = 0.039$), but this association was not confirmed after adjustment for age, lack of prestroke disability, baseline NIHSS score and OTT ≤90 min (Table 3).

3.3. *Night hours*

In comparison to the group admitted during regular working hours, patients admitted during nighttime were younger (median 64 vs. 69 years, $p < 0.001$) and less frequently had a history of hypertension (61.5% vs. 72.6%, $p = 0.026$). Despite similar median stroke severity, they had a lower proportion of mild strokes (Table 1). There were no differences in OTT, DNT, the rate of sICH, neurological improvement and mortality (Table 2). However, the proportion of patients with no residual deficit (mRS 0) after 3 months was lower in patients admitted during night hours (6.6% vs. 15.3%, $p = 0.045$) (Fig. 2). The tendency for lower rate of favorable outcome became significant after adjustment for age, lack of prestroke disability, baseline NIHSS score, and OTT ≤90 min (OR 0.53, 95% CI: 0.29–0.95) (Tables 2 and 3).

4. Discussion

In Poland, intravenous thrombolysis started in October 2003. Since then, many Polish stroke centers have voluntarily joined the SITS registry. Participation in stroke registries is also recommended by the national guidelines [1]. Thrombolysis was initially funded by The National Program for Prevention and Treatment of Cardiovascular Diseases – POLKARD [23]. In 2009, alteplase became reimbursed for stroke by the National Health Fund and the original 3-hour time window was extended to 4.5 h in autumn 2010 [24]. Although the organization of Polish stroke care has been constantly improving [25], the relatively high 3-month mortality rate after thrombolysis [26] reminds that there is still much to be done.

To our knowledge, this is the first nationwide study that uses multivariate methodology and a common reference (i.e. admissions during regular working hours) to simultaneously evaluate the safety, effectiveness and logistics of intravenous thrombolysis for stroke in patients admitted during out-of-office hours, non-working days, and night hours.

Weekend hospital admissions increase the risk of death in both emergency and elective patients [27], including those in intensive care units (ICU) [28]. However, the ICU mortality of nighttime admissions does not seem to exceed the mortality of daytime admissions [28]. In stroke, the time of onset of symptoms shows a circadian pattern with the highest occurrence in the morning, which may partially explain the low proportion of nighttime admissions [29]. A post hoc analysis of the National Institute of Neurological Disorders and Stroke (NINDS) trial showed that the benefit from intravenous thrombolysis did not depend on the time of stroke onset. However, the rate of sICH was the highest in patients who had stroke between 00.00 and 04.00 h [15]. According to our findings, patients admitted at out-of-office hours and on non-working days appear to be very similar to patients admitted during regular working hours, both in terms of baseline characteristic and outcome. The tendency for a lower proportion of mild strokes may correspond with the higher proportion of the hyperdense artery sign, but it does not seem to modify the effect of thrombolysis.

According to a large multicenter study conducted in the USA between 2003 and 2007, stroke patients admitted at out-of-office hours had higher in-hospital morality, despite only minor differences in the quality of care [13]. Studies comparing thrombolysis administered out-of-office hours and during regular hours agree on the similar baseline characteristics of patients, but provide conflicting results on mortality [14,30].

Stroke patients admitted at weekends are also less likely to receive care in line with the current guidelines [5]. Compared to weekday admissions, their thrombolysis rate tends to be lower [6–8,31,32] and the outcome is either similar [6,7,31,32] or worse [8–11]. In Poland, the weekend phenomenon has been addressed in a large analysis of 19 667 unselected ischemic stroke patients admitted between June 2004 and June 2005 to 78 centers participating in the POLKARD Hospital Stroke Registry [12]. In comparison to weekday admissions, patients admitted at the weekends had increased early mortality and a higher rate of combined early mortality and dependency. Thrombolysis was not addressed in this study, because at that time it was rarely used (<1% of ischemic stroke patients nationwide). However, studies concentrating on patients treated with rtPA show no deleterious effect of the weekend admission on outcome, which is also confirmed by our analysis [7,31].

Strokes occurring during sleep are usually more severe and have worse outcome than other strokes [33,34]. In our material, patients admitted at nighttime were younger, more frequently without preexisting disability, and without hypertension. However, they were less likely to achieve favorable 3-month outcome. Previous studies agree on the younger age [7,16]. It has been also suggested that stroke patients treated with rtPA during night hours have a higher rate of sICH [16] despite fewer vascular risk factors or they are less frequently discharged in a good clinical state [7]. On the whole, it may be advisable to pay more attention to patients admitted at nighttime, but there is no reason to refrain from thrombolysis in eligible cases.

In comparison to patients admitted during regular hours, the proportions of those treated within 90 min from the stroke onset were lower in all evaluated groups. Considering the similar rate of DNT ≤60 min, it may be assumed that increased delays were most likely due to prolonged prehospital phase. It concurs with a post hoc analysis of the NINDS trial, showing that patients with the onset of symptoms between 00.00 and 06.00 h are less likely to be treated within 90 min [15]. However, an analysis of the circadian variation of thrombolysis in the SITS-EAST population by Korv et al. [16] demonstrated that both mean OTT and mean DNT were about 10 minutes longer in the nighttime strokes.

4.1. *Study limitations*

The study is based on data from a voluntary registry of stroke patients treated with rtPA. Therefore, it was not possible to determine the reasons for missing data, to establish the rate of thrombolysis in particular time periods or to identify factors deterring the physician on duty from administering rtPA. We may also not exclude a selection bias. However, the rate of patients admitted between 23.00 and 06.00 h is similar to the rate observed in the NINDS trial [15] and a German stroke registry [7]. To minimize the influence of confounders, we used multivariate logistic regression adjusted for age, lack of prestroke disability, baseline NIHSS score, and OTT $\leq$90 min. On the contrary, the registry reflects real life clinical practice of Polish stroke centers.

5. Conclusions

1. There is no such thing as a bad time for intravenous thrombolysis.
2. The safety and effectiveness of thrombolysis seem not to depend on the time of admission and associated disparities in the availability of additional diagnostic equipment and experienced staff. All stroke units in Poland should feel confident about applying the treatment nonstop 24/7.
3. It may be reasonable to pay more attention to patients admitted at nighttime.
4. It is necessary to increase the thrombolytic awareness in patients and ambulance staff to shorten the prehospital delays during the non-regular working hours.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

Appendix

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

II Klinika Neurologiczna IPiN, Warsaw (A. Kobayashi – 301), SP ZZOZ in Sandomierz (P. Sobolewski – 162); Szpital Uniwersytecki nr 2, Bydgoszcz (P. Lisewski – 142); Wojewódzki Zespół Neuropsychiatryczny, Opole (S. Romanowicz – 123); Pomorskie Centrum Traumatologii, Gdańsk (W. Fryze – 108); Uniwersyteckie Centrum Kliniczne, Gdańsk (W. Nyka – 69); Szpital Wojewódzki nr 2, Rzeszów (M. Zięba – 63); CSK MSWiA, Warszawa (M. Dorobek – 55); Szpital Wolski, Warszawa (A. Kuczyńska-Zardzewiały – 45); Szpital Specjalistyczny, Końskie (M. Fudała – 43); SP CSK SUM, Katowice (G. Opala – 42); Szpital Specjalistyczny, Piła (M. Wiszniewska – 36); Szpital Powiatowy, Skarżysko-Kamienna (J. Stoiński – 35); Wojewódzki Szpital Podkarpacki, Krosno (R. Jucha – 20); Szpital Specjalistyczny, Siedlce (P. Kwiatkowski – 20); Wojewódzki Szpital Zespolony, Konin (H. Krupczyńska – 20), Szpital Kolejowy, Pruszków (J. Pniewski – 15); I Klinika Neurologiczna IPiN, Warszawa (P. Richter – 12); Szpital Wojewódzki, Poznań (J.Michalska – 11); Szpital Specjalistyczny, Kościerzyna (A. Walczak – 9); Uniwersytecki Szpital Kliniczny, Białystok (W. Drozdowski – 9), Szpital Powiatowy, Ostrowiec Świętokrzyski (A. Wesek – 8); SP CSK WUM, Warszawa (H. Kwieciński† – 7); WIM, Warszawa (J. Stępień – 1); Dolnośląski Szpital Specjalistyczny, Wrocław (K. Gurański – 4); Wojewódzki Specjalistyczny Zespół Opieki Zdrowotnej, Kielce (H. Prędota-Panecka – 3), Wojewódzki Szpital Specjalistyczny, Olsztyn (A. Tutaj – 1).

REFERENCES

[1] Grupa Ekspertów Sekcji Chorób naczyniowych Polskiego Towarzystwa Neurologicznego. Postępowanie w udarze mózgu. Neurol Neurochir Pol 2012;46(Suppl. 1).
[2] Ringleb A, Bousser M-G, Ford G, Bath P, Brainin M, Caso V, et al. European Stroke Organization guidelines for management of ischaemic stroke and transient ischaemic attack; 2009, Available from: http://www.eso-stroke.org/pdf/ESOGuidelines_update_Jan_2009.pdf [accessed 30.11.12].
[3] Jauch E, Saver J, Adams H, Bruno A, Connors JJ, Demaerschalk B, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870–947.
[4] Manfredini R, Boari B, Salmi R. Higher stroke mortality on weekends: are all strokes the same? Stroke 2007; 38:e112.
[5] Rudd AG, Hoffman A, Down C, Pearson M, Lowe D. Access to stroke care in England, Wales and Northern Ireland: the effect of age, gender and weekend admission. Age Ageing 2007;36:247–55.
[6] Hoh BL, Chi Y-Y, Waters MF, Mocco J, Baker FG. Effect of weekend compared with weekday stroke admission on thrombolytic use, in-hospital mortality, discharge disposition, hospital charges, and length of stay in the Nationwide Inpatient Sample Database, 2002 to 2007. Stroke 2010;41:2323–8.
[7] Jauss M, Schütz HJ, Tanislav C, Misselwitz B, Rosenow F. Effect of daytime, weekday and year of admission on outcome in acute ischaemic stroke patients treated with thrombolytic therapy. Eur J Neurol 2010;17:555–61.
[8] Palmer WL, Bottle A, Davie C, Vincent C, Aylin P. Dying for the weekend: a retrospective cohort study on the

association between day of hospital presentation and the quality and safety of stroke care. Arch Neurol 2012;69:835–7.
[9] Saposnik G, Baibergenova A, Bayer N, Hachinski V. Weekends: a dangerous time for having a stroke? Stroke 2007;38:1211–5.
[10] Janszky I, Ahnve S, Ljung R. Weekend versus weekday admission and stroke outcome in Sweden from 1968 to 2005. Stroke 2007;38:e94.
[11] Turin TC, Kita Y, Rumana N, Ichikawa M, Sugihara H, Morita Y, et al. Case fatality of stroke and day of the week: is the weekend effect an artifact? Takashima stroke registry, Japan (1988–2003) Cerebrovasc Dis 2008;26:606–11.
[12] Niewada M, Jezierska-Ostapczuk A, Skowrońska M, Sarzynska-Dlugosz I, Czlonkowska A. Weekend versus weekday admissions in Polish stroke centres – could admission day affect prognosis in Polish ischaemic stroke patients? Neurol Neurochir Pol 2012;46:15–21.
[13] Reeves MJ, Smith E, Fonarow G, Pan W, Schwamm L. Off-hour admission and in-hospital stroke case fatality in the get with the guidelines-stroke program. Stroke 2009;40:569–76.
[14] Bodenant M, Leys D, Debette S, Cordonnier C, Dumont F, Henon H, et al. Intravenous thrombolysis for acute cerebral ischaemia: comparison of outcomes between patients treated at working versus nonworking hours. Cerebrovasc Dis 2010;30:148–56.
[15] Rhoney DH, Coplin WM, Lin Y, Frankel M, Lyden P, Levine S. Time of day, outcome, and response to thrombolytic therapy: the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Trial experience. J Stroke Cerebrovasc Dis 2010;19:40–8.
[16] Kõrv J, Vibo R, Kadlecová P, Kobayashi A, Czlonkowska A, Brozman M, et al. Benefit of thrombolysis for stroke is maintained around the clock: results from the SITS-EAST Registry. Eur J Neurol 2013. epub ahead of print.
[17] Wahlgren N, Ahmed N, Dávalos A, Ford G, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275–82.
[18] Karlinski M, Kobayashi A, Mikulik R, Mikulik R, Sanak D, Wahlgren N, et al. Intravenous alteplase in ischemic stroke patients not fully adhering to the current drug license in Central and Eastern Europe. Int J Stroke 2012;7:615–22.
[19] Karliński M, Kobayashi A, Litwin T, Fryze W, Romanowicz S, Glonek M, et al. Intravenous thrombolysis for acute ischaemic stroke in patients not fully adhering to the European license in Poland. Neurol Neurochir Pol 2012;46:3–14.
[20] European Medicines Agency (EMEA). Actilyse. Available from: http://www.ema.europa.eu/pdfs/human/referral/Actilyse/334602en.pdf [cited 30.11.12].
[21] Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998;352:1245–51.
[22] Strbian D, Sairanen T, Meretoja A, Pitkanierni J, Putaala J, Salonen O, et al. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. Neurology 2011;77:341–8.
[23] Czlonkowska A, Kobayashi A, Skowronska M, Nieweda M, Sarzynska-Dlugosz I. Thrombolysis for stroke in Poland: first 2 years of experience. Int J Stroke 2006;1:111–2.
[24] Urząd Rejestracji Produktów Leczniczych Wyrobów Medycznych i Produktów Biobójczych. Rejestracja Actilyse w Polsce. Available from: http://leki-informacje.pl/lek/charakterystyka-szczegolowa/1489,actilyse-10.html [cited 30.11.12].
[25] Sarzynska-Dlugosz I, Skowronska M, Czlonkowska A. Development of the stroke unit network in Poland – current status and future requirements. Neurol Neurochir Pol 2007;41:107–12.
[26] Kobayashi A, Czlonkowska A, Ahmed N, Romanowicz S, Blonek M, Nyka W, et al. Intravenous recombinant tissue plasminogen activator for acute stroke in Poland: an analysis based on the Safe Implementation of Thrombolysis in Stroke (SITS) Registry. Acta Neurol Scand 2010;122:229–36.
[27] Mohammed MA, Sidhu KS, Rudge G, Stevens A. Weekend admission to hospital has a higher risk of death in the elective setting than in the emergency setting: a retrospective database study of national health service hospitals in England. BMC Health Serv Res 2012;12:87.
[28] Cavallazzi R, Marik PE, Hirani A, Pachinburavan M, Vasu T, Leiby B. Association between time of admission to the ICU and mortality: a systematic review and metaanalysis. Chest 2010;138:68–75.
[29] Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. Stroke 1998;29:992–6.
[30] Haeusler KG, Gerischer LM, Vatankhah B, Audebert H, Nolte C. Impact of hospital admission during nonworking hours on patient outcomes after thrombolysis for stroke. Stroke 2011;42:2521–5.
[31] Albright KC, Raman R, Ernstrom K, Hallevi H, Martin-Schild S, Meyer B, et al. Can comprehensive stroke centers erase the "weekend effect"? Cerebrovas Dis 2009;27:107–13.
[32] Kazley AS, Hillman DG, Johnston KC, Simpson K. Hospital care for patients experiencing weekend vs weekday stroke. Arch Neurol 2010;67:39–44.
[33] Jiménez-Conde J, Ois A, Rodríguez-Campello A, Gomis M, Roquer J. Does sleep protect against ischemic stroke? Less frequent ischemic strokes but more severe ones. J Neurol 2007;254:782–8.
[34] Kim BJ, Lee S-H, Shin C-W, Ryu W-S, Kim C, Yoon B-W. Ischemic stroke during sleep: its association with worse early functional outcome. Stroke 2011;42:1901–6.