Analyses of the Turkish National Intravenous Thrombolysis Registry

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Background: The relatively late approval of use of recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke in Turkey has resulted in obvious underuse of this treatment. Here we present the analyses of the nationwide registry, which was created to prompt wider use of intravenous thrombolysis, as well as to monitor safe implementation of the treatment in our country. *Methods:* Patients were registered prospectively in our database between 2006 and 2013. Admission and 24-hour National Institutes of Health Stroke Scale and 3-month modified Rankin Scale scores were recorded. A "high-volume center" was defined as a center treating 10 or more patients with rt-PA per year. *Results:* A total of 1133 patients were enrolled into the registry by 38 centers in 18 cities. A nearly 4-fold increase in the study population and in the number of participating centers was observed over the 6 years of the study. The mean baseline NIHSS score was 14.5 ± 5.7, and the prevalence of symptomatic hemorrhage was 4.9%. Mortality at 3 months decreased from 22% to 11% in the 6 years of enrollment, and 65% of cases were functionally independent. Age older than 70 years, an NIHSS score higher than 14 upon hospital admission, and intracranial hemorrhage were independently associated with mortality, and being treated in a high-volume center was related to good outcome. *Conclusions:* We observed a decreasing trend in mortality and an acceptable prevalence of symptomatic hemorrhage over 6 years with continuous addition of new centers to the registry. The first results of this prospective study are encouraging and will stimulate our efforts at increasing the use of intravenous thrombolysis in Turkey. **Key Words:** Intravenous thrombolysis—acute ischemic stroke—thrombolytic therapy—acute stroke treatment.

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Introduction

Stroke is the second leading cause of death in Turkey, accounting for 15% of all deaths, and has the third place in loss of disability adjusted life years estimated with a rate of 5.9%.[1] Although stroke patients receive optimal treatment in many accredited centers, there are difficulties in providing best-practice care because of the disparities of infrastructure between hospitals throughout the country.

Thrombolytic treatment improves functional outcome after acute ischemic stroke (AIS) and is a first-line treatment worldwide.[2] The relatively late approval of use of recombinant tissue plasminogen activator (rt-PA) for AIS in Turkey has resulted in obvious underuse of this treatment.

Important goals for creating a nationwide registry in Turkey were to prompt wider use of rt-PA as well as to monitor safe implementation of the only available AIS treatment.

Materials and Methods

rt-PA for treatment of AIS in Turkey was approved in 2006. A prospective multicenter hospital-based cohort study was designed and undertaken in centers around the country. As the national regulatory agency did not require a compulsory data collection, patients from only voluntary centers could be included. Consecutive patients with AIS who underwent intravenous thrombolysis and who were admitted to participating institutions between November 2006 and January 2013 were included in the registry.

Inclusion criteria were (1) baseline stroke severity according to a National Institutes of Health Stroke Scale (NIHSS) score higher than 4, (2) no imaging (computed tomography [CT]/magnetic resonance imaging [MRI]) evidence of intracranial hemorrhage, (3) onset of stroke at less than 3 hours (updated to <4.5 hours in 2012), and (4) age range of 18-80 years (based on regulations set by the National Regulatory Agency) and standard exclusion criteria were applied.[3]

The following data were recorded: age; sex; medical history; presentation; time from onset of symptoms to hospital admission; door-to-needle time (DTNT); imaging methods (baseline and follow-up); and admission site (intensive care unit, stroke unit, neurology ward, and neurointensive care unit). All data entries were performed by the local stroke neurologist.

Intravenous thrombolysis with rt-PA was administered less than 3 hours after symptom onset at the standard dose of .9 mg/kg.[3] Written informed consent was obtained from patients or their relatives. Stroke subtype, determined after diagnostic evaluation, was classified as "cardioembolic," "large vessel," "small vessel," "other determined pathogenesis," or "cryptogenic" using Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. All patient information was entered into an Internet-based form. University of Dokuz Eylül (Izmir, Turkey) was the coordinating center for all registration steps as well as frequently reminding all centers to enter and update their data.

Outcome Measures

Early neurological improvement was assessed 24 hours after thrombolysis using the NIHSS. The following cutoff levels were identified: (1) improvement of NIHSS score by 4 points or higher,[2] (2) improvement by 20%[4] from the baseline NIHSS score, and (3) improvement by 40%[5] from the baseline NIHSS score. Functional outcome was measured at 3 months by the modified Rankin Scale (mRS). The main outcome measure was independence, defined as an mRS score of 0-2 on day 90. "Symptomatic intracranial hemorrhage" was defined as a neurological deterioration causing a 4-point or more worsening on the NIHSS score causally related to intracranial hemorrhage detected by CT/MRI at 36 hours or less after the initiation of thrombolysis.

To assess the effects of a potential learning curve for each center, different cutoff levels for patient numbers admitted per year (e.g., ≥5, ≥7, ≥10) were examined for different variables (e.g., DTNT, protocol deviation, and mortality).

Statistical Analyses

χ^2 was used for the comparison of categorical variables. Student's *t*-test was used for the comparison of continuous variables. A multivariate logistic regression model was employed for prediction of mortality. Independent variables included in the logistic regression model were age older than 70 years, NIHSS score higher than 14, intracranial hemorrhage, and number of patients admitted per year. STATA v11 was used for statistical analyses (StataCorp, College Station, TX). A *P* value less than .05 was considered significant.

Results

Data were collected from 38 centers in 18 cities in Turkey (Fig 1). A total of 1208 patients were entered into the registry during the study period. Sixty-six patients had missing data (on DTNT or outcome) and 9 patients with onset of stroke for more than 4.5 hours were excluded from further analyses. However, cases in which there were uncertainties about the type of baseline imaging (CT or MRI, 8 patients) and area in hospital where rt-PA was applied (emergency room versus intensive care unit, 36 patients) were kept in the analysis. Patients with protocol deviations (242 patients) were also included in the final analysis. This cohort comprised 71 patients aged older than 80 years and 171 patients treated 3.0-4.5 hours until

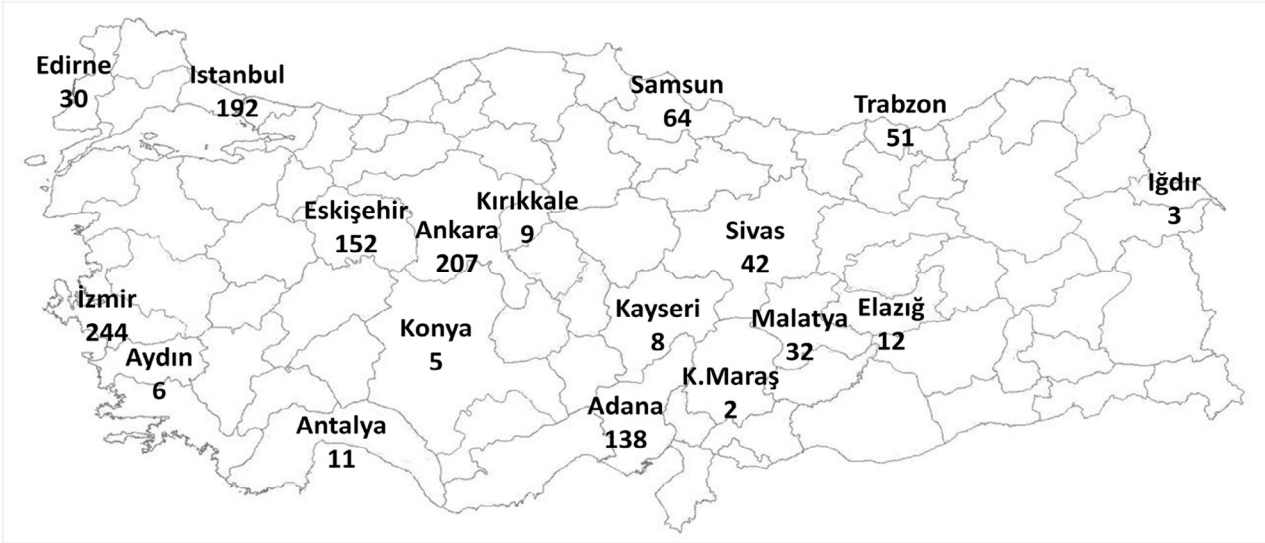

Figure 1. *Distribution of registered patients throughout the country.*

extension of the therapeutic window in 2012. Finally, 1133 patients remained for the primary analysis. Long-term outcome was assessed in 688 patients because mRS data at 3 months were not available for the remaining subjects.

The mean age of the study cohort was 64 ± 13 years, 653 (57%) were females, and the mean baseline NIHSS score was 14.5 ± 5.7 (Table 1). Of these, 898 (79.1%) patients underwent CT, 89 (7.8%) underwent MRI, and 140 (12.2%) had CT and MRI. A "high-volume center" was defined as a center applying rt-PA to 10 or more patients per year. Patient distribution between high- and low-volume centers was fairly well balanced (577 versus 556, respectively). The increasing number of centers participating in the registry over time, distribution of survival, overall mortality, and symptomatic hemorrhage according to enrollment years and DTNT according to years and high- or low-volume centers are displayed in Figures 2-4. There was a significant difference in data for improvement over 24 hours (i.e., for NIHSS score, decrease of 4 points or higher, 20%, and 40% change from baseline) among patients with mRS scores of 0-2 (84%, 94%, and 83%, respectively) and 2 or higher at 3 months (16%, 6%, and 17%, respectively) ($P < .001$).

Overall, 165 (14.7%) patients died during the 3-month follow-up. All hemorrhage types were associated with mortality in the univariate analysis. Interestingly, high-volume centers demonstrated a higher prevalence of total intracranial hemorrhage but a lower prevalence of symptomatic intracranial hemorrhage and mortality (Table 1). As expected, DTNT was shorter in high-volume centers. Other results for factors associated with clinical outcome in the univariate analysis are listed in Table 1 and those for the multivariate analysis are listed in Table 2.

Multivariate analysis showed that age older than 70 years, an NIHSS score higher than 14, and intracranial hemorrhage were independently associated with high mortality, whereas being treated in high-volume centers was inversely related to mortality (Table 2).

Discussion

This was the first nationwide registry on thrombolysis after the approval of rt-PA for the treatment of AIS in Turkey. A remarkable feature of the present registry has been the growing number of centers and patients since 2006. There was nearly a 4-fold increase in the study population and in the number of centers in 6 years, starting with 55 patients in 12 centers per year in 2007, increasing to 250 patients in 38 centers per year in 2012. Despite the continuous addition of relatively inexperienced centers in the registry, the decreasing prevalence of mortality and acceptable prevalence of symptomatic hemorrhage should be noted.

Early neurological improvement after thrombolysis is widely accepted as a useful predictor of recanalization and favorable functional outcome, but the exact definition of "early neurological improvement" has yet to be clarified.[6] Early neurological improvement can be assessed 2 or 24 hours after rt-PA therapy. Recently, it has been reported that changes in the NIHSS score at 24 hours can predict recanalization better than assessment at 2 hours.[7] The criterion of neurological assessment at 24 hours was accepted during the original design of our registry. In accordance with other published series, nearly half of the patients showed some degree of clinical improvement 24 hours after thrombolysis, and 65% of cases were functionally independent at 3 months. We also observed a significant correlation between improvement in the NIHSS score at 24 hours and functional outcome at 3 months (mRS score of 0-2).

Table 1. *Patient characteristics, clinical variables, and outcome in univariate analysis*

Characteristics	Overall n = 1133 (%)	Fatal n = 165 (%)	Survived n = 968 (%)	*P*	High-volume centers n = 577 (%)	Low-volume centers n = 556 (%)	*P*
Mean age* (SD)	64 (13)	68.7 (11)	63.6 (13)	<.001	63.7 (13)	65 (13)	.09
Sex (F)	653 (57)	89 (54)	564 (58)	.299	343 (59)	310 (56)	.209
Baseline mean NIHSS score* (SD)	14.5 (5.7)	17.6 (5.2)	14 (5.6)	<.001	15.1 (6)	13.8 (5.2)	<.001
Mean time (min)* (SD)							
Symptom onset to hospital	81 (46)	77.8 (46.5)	81.6 (46)	.333	88.7 (49)	73.2 (41)	<.001
Door to needle	69.5 (32.5)	69.3 (34)	69.5 (32)	.928	67 (32)	71 (32)	.026
Symptom onset to needle	150 (43)	147 (44)	151 (43)	.290	155 (44)	144 (42)	<.001
Hemorrhage							
Systemic	34 (3)	16 (9.7)	18 (1.85)	<.001	10 (1.7)	24 (4.3)	.011
Intracranial	253 (22)	50 (30)	203 (21)	.008	150 (26)	103 (18.5)	.003
Symptomatic	55 (4.9)	32 (19)	23 (2.3)	<.001	15 (2.6)	40 (7)	<.001
Baseline							
CT	898 (80)	139 (85)	759 (79)	.061	506 (88)	392 (71)	.001
MRI	89 (7.8)	6 (3.6)	83 (8.5)	.029	12 (2)	17 (14)	.001
Protocol deviation	242 (21)	34 (20)	208 (21)	.904	141 (24)	101 (18)	.05
More than 3 h	171 (15)	23 (2)	148 (15)	.654	100 (17)	71 (12)	.032
More than 80 years old	71 (6)	13 (8)	58 (6)	.355	36 (6)	35 (6)	.969
10 or more patients per year	577 (50.9)	72 (12)	505 (88)	.043			
Less than 10 patients per year	556 (49)	93 (17)	463 (83)				
Stroke subgroups							
Occlusion of the large artery	274 (26)	34 (23)	240 (26)		132 (23)	142 (29)	
Cardioembolism	485 (46)	78 (53)	407 (45)		279 (49)	206 (42)	
Occlusion of the small artery	98 (9.3)	3 (2)	95 (10)	.001	57 (10)	41 (8)	.001
Other	30 (2.8)	1 (1)	29 (3)		24 (4)	6 (1)	
Cryptogenic	166 (15.7)	31 (21)	135 (15)		76 (13)	90 (19)	
Application of thrombolysis							
Emergency service	600 (53)	64 (39)	536 (55)		379 (66)	221 (40)	
Intensive care unit	48 (4)	5 (3)	43 (4)		1 (1)	47 (8)	
Stroke unit	35 (3)	9 (5)	26 (3)	<.001	16 (3)	19 (3)	<.001
Neurology ward	21 (2)	2 (1)	19 (2)		3 (1)	18 (3)	
Neurointensive care unit	383 (34)	73 (44)	310 (32)		161 (28)	222 (40)	
Follow-up							
Stroke unit	223 (20)	21 (13)	202 (21)		145 (25)	78 (14)	
Intensive care unit	57 (5)	11 (7)	46 (5)	<.001	2 (1)	55 (10)	<.001
Neurology ward	152 (14)	9 (6)	143 (15)		19 (3)	133 (24)	
Neurointensive care unit	682 (61)	119 (74)	563 (59)		404 (71)	278 (51)	
Improvement of NIHSS score at 24 h							
4 points or more	610 (54)	43 (26)	567 (59)	<.001	363 (63)	247 (44)	<.001
20%	673 (60)	43 (26)	630 (65)	<.001	388 (67)	285 (51)	<.001
40%	500 (44)	31 (18.7)	469 (48)	<.001	297 (51)	203 (36.5)	<.001
Three-month mRS score (0-2), n = 688	449 (65)	0	448 (68)	<.001	255 (66)	194 (64)	.618

Abbreviations: CT, computed tomography; F, female; mRS, modified Rankin Scale; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation.

High-volume center refers to a center that administers rt-PA to 10 or more patients per year.

*Student's *t*-test.

During the past 20 years, several studies have noted that higher hospital volume is associated with better outcome in general health care.[8,9] There are no accepted definitions of "experienced center" or "high-volume center" for thrombolytic treatment, but "experienced center" was defined by the number of patients treated by rt-PA per year.[10-12] Authors showed that, in centers administering rt-PA in more than 5 patients per year, the overall prevalence of thrombolysis was increased. Another study showed that patients admitted to hospitals with a volume of 50 or more cases per year had significantly shorter delays in administration of rt-PA after arrival at the hospital.[13]

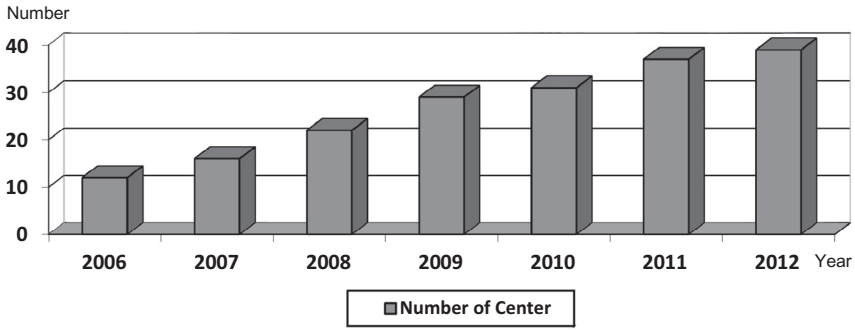

Figure 2. *Number of participating centers to the registry according to years.*

In the present study, high-volume centers (≥10 patients per year) had better outcome for hemorrhage (systemic and symptomatic intracranial) and DTNT in univariate and multivariate analyses. Moreover, the experience of treating 10 or more patients per year was associated with decreased mortality in the multivariate analysis.

The median DTNT is recommended to be 60 minutes or less.[14,15] This critical time limit was reached at the end of the fourth year of our registry and, despite the addition of new centers, the mean treatment time remained at 69 minutes. DTNT, age older than 80 years, sex, and time from symptom onset to treatment of 3.0-4.5 hours had no negative effect on overall mortality. All-cause mortality decreased from 22% to 11% in the 6 years of enrollment. High-volume centers made more protocol deviations (more patients included after 3 hours from symptom onset) than others, but had better DTNT and fewer symptomatic hemorrhages. Furthermore, similar

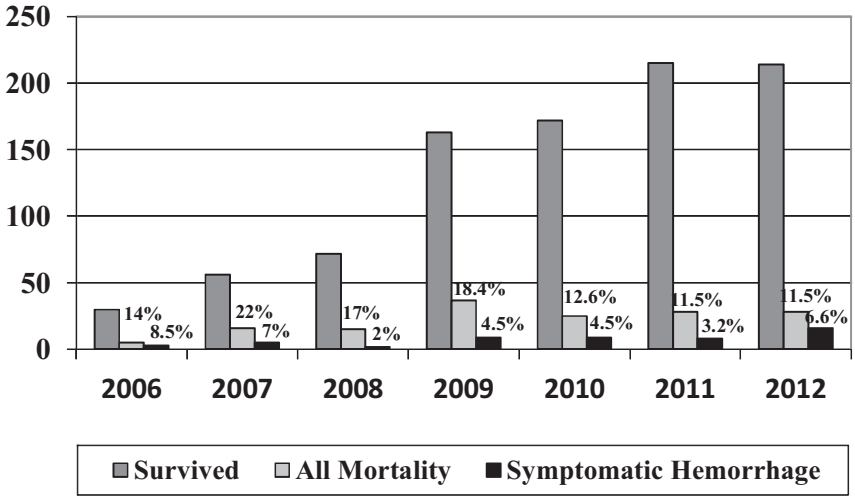

Figure 3. *Outcome: prevalence of all-cause mortality, survival, and symptomatic hemorrhage according to years.*

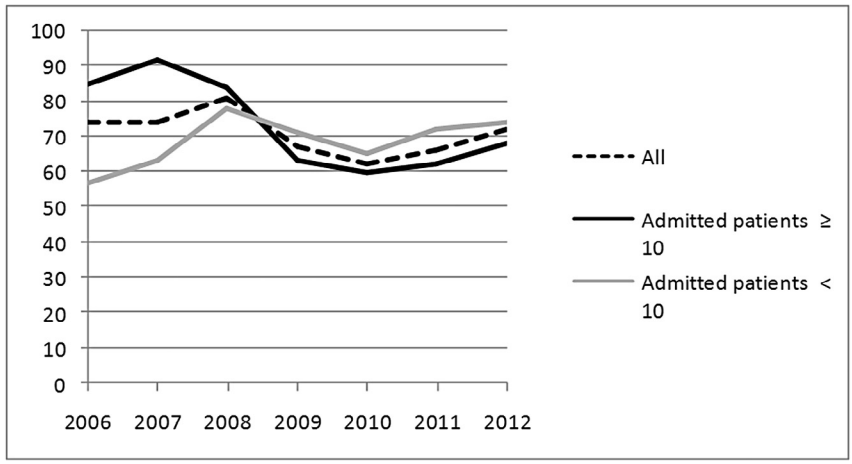

Figure 4. *Door-to-needle-time (minutes) according to years and high- or low-volume centers (admitted refers to patients treated with rt-PA). Abbreviation: rt-PA, recombinant tissue plasminogen activator.*

Table 2. *Multivariate (adjusted) analysis for mortality*

	OR	CI	*P*
Age (>70 years)	1.8	1.29-2.58	.001
NIHSS score (>14)	4.8	3.11-7.53	<.001
Intracranial hemorrhage	1.5	1.29-2.58	.029
High-volume center	.65	.46-.93	.019

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; rt-PA, recombinant tissue plasminogen activator.

High-volume center refers to a center that administers rt-PA to 10 or more patients per year.

3-month results in high- and low-volume centers are encouraging because inexperienced centers had as many good results as more experienced centers.

Half of the patients received thrombolysis on-site (i.e., in the emergency room under the direct supervision of the attending neurologist). This practice allowed centers to reduce the delay in treatment in their particular settings and may have been reflected in greater numbers of surviving patients (55% versus 39% for survivors versus mortality, respectively). The imaging modality was left to the discretion of each center according to its ability to undertake imaging within the shortest time period, and most centers used CT.

One of the limitations of the present study was the lack of detailed information on risk factors. Our primary aim was to monitor the safety of treatment over a large number of centers in the most practical manner, so only data on stroke classification (TOAST) were collected centrally. Another drawback was the lack of 3-month mRS data in 445 (39%) of 1133 patients.

In conclusion, the aim of safe and broad implementation of the only available AIS treatment has been relatively reached and is still an ongoing process. The first results of this prospective registry are encouraging and stimulate our efforts at increasing participating centers in our country.

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Appendix

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References

1. Ozturk S. Epidemiology and the global burden of stroke-situation in Turkey. World Neurosurg 2014;81:5-6.
2. Wahlgren N, Ahmed N, Dávalos A, 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;369:275-282.
3. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.
4. Nam HS, Lee KY, Han SW, et al. Prediction of long-term outcome by percent improvement after the first day of

thrombolytic treatment in stroke patients. J Neurol Sci 2009;281:69-73.
5. Mikulik R, Ribo M, Hill MD, et al. Accuracy of serial National Institutes of Health Stroke Scale scores to identify artery status in acute ischemic stroke. Circulation 2007;115:2660-2665.
6. Kharitonova TV, Melo TP, Andersen G, et al. Importance of cerebral artery recanalization in patients with stroke with and without neurological improvement after intravenous thrombolysis. Stroke 2013;44:2513-2518.
7. Kharitonova T, Mikulik R, Roine RO, et al. Association of early National Institutes of Health Stroke Scale improvement with vessel recanalization and functional outcome after intravenous thrombolysis in ischemic stroke. Stroke 2011;42:1638-1643.
8. Hannan EL. The relation between volume and outcome in health care. N Engl J Med 1999;340:1677-1679.
9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med 2002;137:511-520.
10. Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: The Cleveland area experience. JAMA 2000;283:1151-1158.
11. Heuschmann PU, Berger K, Misselwitz B, et al. Frequency of thrombolytic therapy in patients with acute ischemic stroke and the risk of in-hospital mortality: the German Stroke Registers Study Group. Stroke 2003;34:1106-1113.
12. Tanne D, Bates VE, Verro P, et al. Initial clinical experience with i.v. tissue plasminogen activator for acute ischemic stroke. A multicentre survey. Neurology 1999;53:424.
13. Bray BD, Campbell J, Cloud GC, et al. Bigger, faster? Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. Stroke 2013;44:3129-3135.
14. Fonarow GC, Smith EE, Saver JL, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. Circulation 2011;123:750-758.
15. Alberts MJ, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. JAMA 2000;283:3102-3109.