JoS JOURNAL OF STROKE

Journal of Stroke 2021;23(1):135-138
https://doi.org/10.5853/jos.2020.04658

Letter to the Editor

Golden Hour Thrombolysis in Acute Ischemic Stroke: The Changing Pattern in South Korea

Hyunsoo Kim,[a] Joon-Tae Kim,[a] Ji Sung Lee,[b] Beom Joon Kim,[c] Jong-Moo Park,[d] Kyusik Kang,[d] Soo Joo Lee,[e] Jae Guk Kim,[e] Jae-Kwan Cha,[f] Dae-Hyun Kim,[f] Tai Hwan Park,[g] Sang-Soon Park,[g] Kyung Bok Lee,[h] Jun Lee,[i] Keun-Sik Hong,[j] Yong-Jin Cho,[j] Hong-Kyun Park,[j] Byung-Chul Lee,[k] Kyung-Ho Yu,[k] Mi Sun Oh,[k] Dong-Eog Kim,[l] Wi-Sun Ryu,[l] Jay Chol Choi,[m] Jee-Hyun Kwon,[n] Wook-Joo Kim,[n] Dong-Ick Shin,[o] Sung Il Sohn,[p] Jeong-Ho Hong,[p] Man-Seok Park,[a] Kang-Ho Choi,[a] Ki-Hyun Cho,[a] Juneyoung Lee,[q] Hee-Joon Bae[c]

[a]Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea
[b]Clinical Research Center, Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[c]Department of Neurology, Cerebrovascular Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[d]Department of Neurology, Nowon Eulji Medical Center, Eulji University, Seoul, Korea
[e]Department of Neurology, Daejeon Eulji Medical Center, Eulji University, Daejeon, Korea
[f]Department of Neurology, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Korea
[g]Department of Neurology, Seoul Medical Center, Seoul, Korea
[h]Department of Neurology, Soonchunhyang University Hospital, Soonchunhyang University College of Medicine, Seoul, Korea
[i]Department of Neurology, Yeungnam University Medical Center, Yeungnam University College of Medicine, Daegu, Korea
[j]Department of Neurology, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea
[k]Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea
[l]Department of Neurology, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, Goyang, Korea
[m]Department of Neurology, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Korea
[n]Department of Neurology, University of Ulsan College of Medicine, Ulsan, Korea
[o]Department of Neurology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea
[p]Department of Neurology, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea
[q]Department of Biostatistics, Korea University College of Medicine, Seoul, Korea

Dear Sir:

Intravenous tissue plasminogen activator (IV-tPA) is pivotal for the treatment of acute ischemic stroke; however, the benefit of IV-tPA treatment declines rapidly soon after stroke onset.[1] These results support intensive efforts to reduce both onset-to-treatment (OTT) time and door-to-treatment (DTT) time and serve as a basis for establishing an in-hospital and prehospital stroke care system. As these efforts require substantial expenditures of labor and capital, more real-world data are needed to assess the effect of golden hour thrombolysis for acute ischemic stroke. Moreover, understanding the current status and secular changes in IV-tPA treatment will be important to establish an appropriate stroke care system in the future. Therefore, we investigated the effect of golden hour thrombolysis and secular changes in time-to-treatment variables for IV-tPA for acute ischemic stroke by analyzing a prospective registry of 16 stroke centers in South Korea.

This study was based on data from the Clinical Research Collaboration for Stroke in Korea registry of consecutive patients with acute ischemic stroke or transient ischemic attack. From the database, we analyzed the data of patients who were treated with IV-tPA between April 2008 and March 2019. A detailed description of the enrollment process and data collection process is shown in Supplementary Figure 1 and the Supplementary methods. The time metrics, starting from onset or arrival, were defined as follows: (1) onset-to-door (OTD) time was defined as the time from onset (when the patient was last known to be well) to arrival; (2) OTT time was defined as the time from onset to IV-tPA treatment; and (3) DTT time was de-

Table 1. Association of OTT time with functional outcomes at 3 months

Variable	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
mRS score of 0–2 at 3 months				
Binary				
OTT ≤60 min	1.28 (0.99–1.64)	0.059	1.35 (1.01–1.81)	0.043
OTT 61–270 min	Reference		Reference	
Categorical				
OTT ≤60 min	1.59 (1.20–2.10)	0.001	1.71 (1.24–2.35)	0.001
OTT 61–120 min	1.46 (1.24–1.71)	<0.001	1.45 (1.20–1.74)	<0.001
OTT 121–180 min	1.18 (1.00–1.40)	0.056	1.23 (1.01–1.50)	0.039
OTT 181–270 min	Reference		Reference	
Continuous				
OTT, continuous, every 30 min	0.92 (0.89–0.95)	<0.001	0.92 (0.89–0.96)	<0.001
mRS distribution (favorable shift)				
Binary				
OTT ≤60 min	1.30 (1.05–1.61)	0.015	1.34 (1.08–1.67)	0.008
OTT 61–270 min	Reference		Reference	
Categorical				
OTT ≤60 min	1.54 (1.22–1.95)	<0.001	1.59 (1.25–2.03)	<0.001
OTT 61–120 min	1.36 (1.18–1.56)	<0.001	1.32 (1.14–1.53)	<0.001
OTT 121–180 min	1.10 (0.95–1.28)	0.205	1.14 (0.98–1.32)	0.100
OTT 181–270 min	Reference		Reference	
Continuous				
OTT, continuous, every 30 min	0.93 (0.90–0.95)	<0.001	0.93 (0.91–0.96)	<0.001

Adjustment variables: age, male sex, initial National Institutes of Health Stroke Scale (NIHSS) score, history of stroke, hypertension, diabetes mellitus, atrial fibrillation, prior statin use, systolic blood pressure, glucose, tissue plasminogen activator dose, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.
OTT, onset-to-treatment; OR, odds ratio; CI, confidence interval; mRS, modified Rankin Scale.

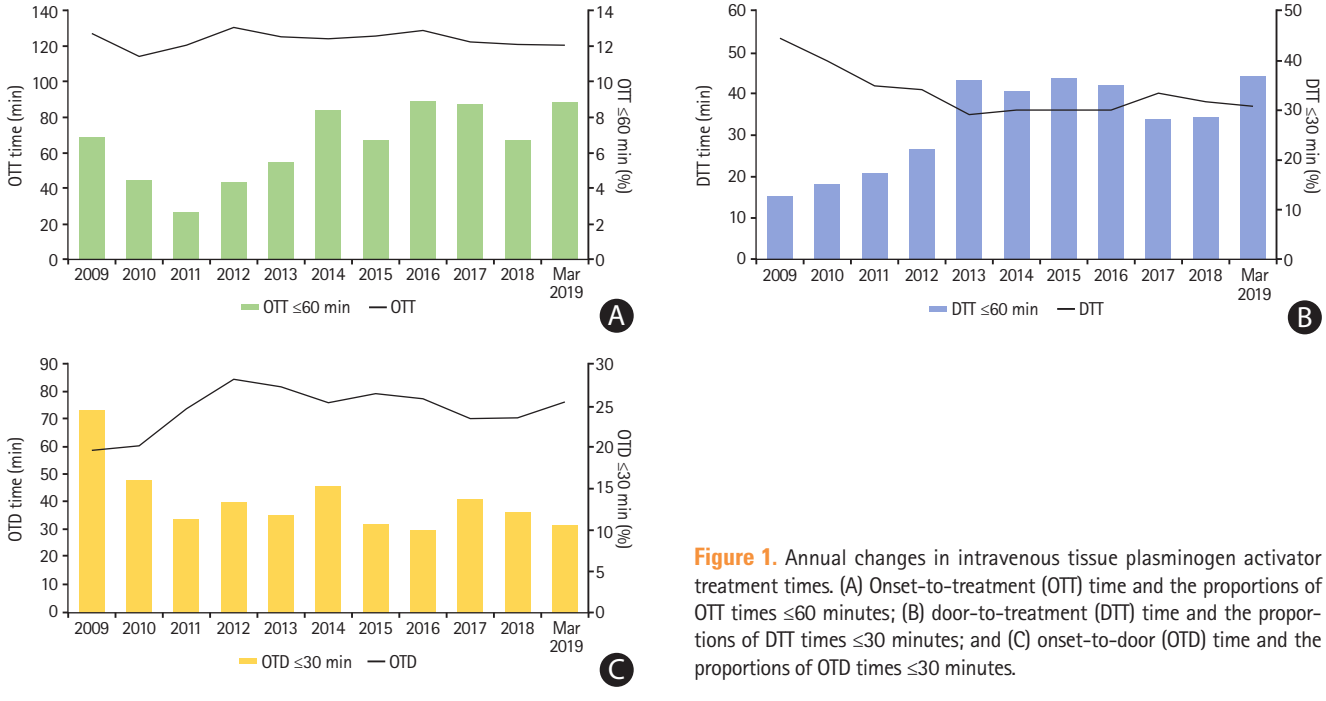


Figure 1. Annual changes in intravenous tissue plasminogen activator treatment times. (A) Onset-to-treatment (OTT) time and the proportions of OTT times ≤60 minutes; (B) door-to-treatment (DTT) time and the proportions of DTT times ≤30 minutes; and (C) onset-to-door (OTD) time and the proportions of OTD times ≤30 minutes.

https://doi.org/10.5853/jos.2020.04658

fined as the time from arrival to IV-tPA treatment. The primary outcome was a good functional outcome at 3 months (a modified Rankin Scale [mRS] score of 0–2). Other outcomes of interest are described in the Supplementary methods.

Multivariable logistic regression models using generalized linear mixed models to account for the effect of hospital (using a random intercept model) were used to explore the relationship between OTT time and the clinical outcome of interest. In addition, we explored the temporal trends in the OTT time, DTT time, and OTD time by calendar year.

A total of 4,248 patients (mean age 67.6±12.6 years; 62% men) were included. In total, 282 (6.6%) patients had an OTT time between 0 and 60 minutes. The general characteristics of patients according to the four OTT windows (0–60, 61–120, 121–180, and 181–270 minutes) are shown in Supplementary Table 1. The associations of OTT windows (as binary, categorical, and continuous variables) with outcomes are shown in Table 1 and Supplementary Table 2. Patients treated within 60 minutes of onset were associated with 35% higher odds of achieving good outcomes at 3 months than those treated beyond 60 minutes of onset (adjusted odds ratio [aOR], 1.35; 95% confidence interval [CI], 1.01 to 1.81). In addition, for every 30-minute delay in treatment, a favorable mRS shift was less likely to occur (OR, 0.93; 95% CI, 0.90 to 0.95) (Supplementary Figure 2).

From April 2008 to March 2019, the proportion of IV-tPA times within the golden hour increased modestly over time, from less than 6.9% in 2009 to 8.8% in 2019, with associations of 12% higher odds for golden hour thrombolysis for every 1-year increase (aOR, 1.12; 95% CI, 1.03 to 1.21; *P*=0.005) (Figure 1 and Supplementary Table 3).

In an analysis of over 4,200 patients treated with IV-tPA from a nationwide multicenter stroke registry in South Korea, golden hour thrombolysis was associated with better functional outcomes at 3 months than later treatment. The risk of death or symptomatic intracerebral hemorrhage was not associated with golden hour thrombolysis. Time to IV-tPA treatment is an important determinant of 90-day functional outcomes in acute ischemic stroke.[2] In previous studies, golden hour thrombolysis was associated with a good functional outcome at discharge and 3 months.[1,3] Therefore, our study supports the previous results on the effects of golden hour thrombolysis in real-world practice.

In addition, we found that annual rates of golden hour thrombolysis have substantially increased since 2009. These results seemed to be related to the decrease in DTT time or the increasing percentages of DTT time within 30 minutes. Efforts to reduce DTT are the main goal of stroke, and our results support the hypothesis that stroke centers implementing quality improvement programs for in-hospital stroke care improve the workflow of tPA treatment.[4-7] Unlike the results of DTT reduction, the proportion of patients with OTD <30 minutes decreased from that in 2009. This might be an unsolved problem in the stroke system in Korea, and further study is warranted.

This study has several limitations. First, the participating centers did not use uniform guidelines for diagnostic evaluation, patient selection, or IV-tPA treatment workflows. Additionally, detailed hospital factors such as door-to-imaging time were not considered in the analyses. Third, we did not include patients who underwent endovascular thrombectomy. As they might have increased stroke severity, this exclusion could have affected the results. Fourth, our statistical adjustments for patient differences may have been incomplete because of residual or unmeasured confounding variables.

In conclusion, our results show that golden hour thrombolysis could improve the chances of a good outcome at 3 months. Although the data supporting the improvement in in-hospital delay for IV-tPA treatment are clear, the results also suggest that additional efforts to implement more advanced stroke care systems are warranted to further improve acute stroke care in South Korea.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2020.04658.

References

1. Kim JT, Fonarow GC, Smith EE, Reeves MJ, Navalkele DD, Grotta JC, et al. Treatment with tissue plasminogen activator in the golden hour and the shape of the 4.5-hour time-benefit curve in the national United States get with the guidelines-stroke population. *Circulation* 2017;135:128-139.
2. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384:1929-1935.
3. Tsivgoulis G, Katsanos AH, Kadlecová P, Czlonkowska A, Kobayashi A, Brozman M, et al. Intravenous thrombolysis for ischemic stroke in the golden hour: propensity-matched analysis from the SITS-EAST registry. *J Neurol* 2017;264:912-920.
4. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt

DL, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *JAMA* 2014;311:1632-1640.
5. Kamal N, Holodinsky JK, Stephenson C, Kashayp D, Demchuk AM, Hill MD, et al. Improving door-to-needle times for acute ischemic stroke: effect of rapid patient registration, moving directly to computed tomography, and giving alteplase at the computed tomography scanner. *Circ Cardiovasc Qual Outcomes* 2017;10:e003242.
6. Kassardjian CD, Willems JD, Skrabka K, Nisenbaum R, Barnaby J, Kostyrko P, et al. In-patient code stroke: a quality improvement strategy to overcome knowledge-to-action gaps in response time. *Stroke* 2017;48:2176-2183.
7. Heo JH, Kim YD, Nam HS, Hong KS, Ahn SH, Cho HJ, et al. A computerized in-hospital alert system for thrombolysis in acute stroke. *Stroke* 2010;41:1978-1983.

Correspondence: Joon-Tae Kim
Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju 61469, Korea
Tel: +82-62-220-6180
Fax: +82-62-228-3461
E-mail: alldelight2@jnu.ac.kr
https://orcid.org/0000-0003-4028-8339

Co-correspondence: Hee-Joon Bae
Department of Neurology, Cerebrovascular Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: +82-31-787-7467
Fax: +82-31-787-4059
E-mail: braindoc@snu.ac.kr
https://orcid.org/0000-0003-0051-1997

Received: November 23, 2020
Revised: January 13, 2021
Accepted: January 14, 2021

This study was supported by a grant (BCRI20020) from Chonnam National University Hospital Biomedical Research Institute. This study was supported by funding (2020ER620200#) from the Research of Korea Centers for Disease Control and Prevention.

The authors have no financial conflicts of interest.

https://doi.org/10.5853/jos.2020.04658

Supplementary methods

Data collection

Demographic, clinical, imaging, and laboratory data were prospectively collected. Baseline data, including National Institutes of Health Stroke Scale (NIHSS) scores, were collected from all patients, and the stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria after complete diagnostic profiling. The following data were directly obtained from the registry database: (1) demographics, (2) medical history, (3) medication, (4) stroke characteristics and acute treatment, (5) laboratory data, and (6) in-hospital treatment data. For continuous variables, the data were imputed to the median values if <5% of the values were missing.

Outcome measures

The other outcomes of interest were the distribution of functional outcomes according to the 3-month modified Rankin Scale (mRS) score, an excellent functional outcome at 3 months (a mRS score of 0–1), symptomatic intracerebral hemorrhage (SICH) within 3 months, and death within 3 months. SICH was defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria as a worsening of neurological status (an increase in NIHSS score of 4 or more) with the appearance of new parenchymal hemorrhage (type 2) on brain imaging that was sufficient to cause neurological deterioration.

Statistical analysis

The following parameters had missing data that were imputed to the median values: onset-to-treatment (OTT) time (0.6%), door-to-treatment (DTT) time (0.6%), body mass index (2.2%), creatinine (0.1%), hemoglobin (0.1%), white blood cell (WBC) count (0.1%), and initial random glucose (0.7%).

The baseline characteristics, workflow time metrics, and outcomes were compared among patients treated in the OTT windows of 0–60, 61–120, 121–180, and 181–270 minutes, and between patients treated within and beyond the golden hour (OTT window of 0–60 minutes). Multivariable logistic regression models using generalized linear mixed models to account for the effect of hospital (using a random intercept model) were used to explore the relationship between OTT and the clinical outcome of interest. The adjusted models were controlled for predetermined variables with clinically relevant associations with the outcome variables: age, male sex, initial NIHSS score, history of stroke, hypertension, diabetes mellitus, atrial fibrillation, pre-stroke statin use, systolic blood pressure, glucose, TOAST subtype, tissue plasminogen activator dose, and workflow time variables (OTT, DTT, and onset-to-door [OTD] times). In addition, we explored the temporal trends in the OTT time (and proportion of OTT times ≤30 minutes), DTT time (and proportion of DTT times ≤30 minutes), and OTD time (and proportions of OTD times ≤30 minutes) by calendar year.

P-values <0.05 were considered statistically significant. Odds ratios and 95% confidence intervals were calculated. Statistical analysis was performed using R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Supplementary Table 1. General patient characteristics according to the time to IV-tPA treatment

Characteristic	OTT ≤60 min	OTT 61–120 min	OTT 121–180 min	OTT 181–270 min	*P*	OTT >60 min	*P*
Number	282	1,764	1,301	901		3,966	
Age (yr)	66.2±13.0	66.7±12.7	68.3±12.6	68.8±12.3	<0.001	67.7±12.6	0.046
Male sex	178 (63.1)	1,122 (63.6)	774 (59.5)	560 (62.2)	0.135	2,456 (61.9)	0.704
Pre-mRS score of 0–1	242 (85.8)	1,552 (88.0)	1,115 (85.7)	778 (86.3)	0.271	3,445 (86.9)	0.586
Initial NIHSS	8 (4–14)	7 (4–13)	6 (4–12)	7 (4–12)	0.001	7 (4–12)	0.016
BMI (kg/m^2)	23.7 (3.4)	23.9 (3.4)	23.4 (3.4)	23.5 (3.5)	0.005	23.6 (3.4)	
Situation					<0.001		0.007
Wake-up	5 (1.8)	44 (2.5)	80 (6.1)	74 (8.2)		198 (5.0)	
During sleep	3 (1.1)	20 (1.1)	41 (3.2)	34 (3.8)		95 (2.4)	
During activity	233 (82.6)	1,452 (82.3)	928 (71.3)	569 (63.2)		2,949 (74.4)	
Unknown	41 (14.5)	248 (14.1)	252 (19.4)	224 (24.9)		724 (18.3)	
Workflow times (min)							
OTT	52 (48–56)	90 (75–103)	150 (135–165)	218 (198–240)	<0.001	130 (92–178)	<0.001
DTT	26 (20–32)	38 (29–50)	42 (30–57)	41 (30–58)	<0.001	40 (29–53)	<0.001
OTD	25 (18–31)	48 (34–63)	105 (85–125)	173 (148–197)	<0.001	80 (48–132)	<0.001
TOAST					0.054		0.025
LAA	61 (21.6)	487 (27.6)	391 (30.1)	278 (30.9)		1,156 (29.1)	
SVO	27 (9.6)	219 (12.4)	155 (11.9)	101 (11.2)		475 (12.0)	
CE	102 (36.2)	568 (32.2)	397 (30.5)	258 (28.6)		1,223 (30.8)	
OE	7 (2.5)	36 (2.0)	23 (1.8)	11 (1.2)		70 (1.8)	
UD	85 (30.1)	454 (25.7)	335 (25.7)	253 (28.1)		1,042 (26.3)	
Previous TIA	4 (1.4)	34 (1.9)	23 (1.8)	11 (1.2)	0.581	68 (1.7)	>0.999
Previous stroke	45 (16.0)	262 (14.9)	239 (18.4)	139 (15.4)	0.063	640 (16.1)	>0.999
History of CAD	32 (11.3)	174 (9.9)	138 (10.6)	87 (9.7)	0.767	399 (10.1)	0.475
History of PAD	0 (0.0)	12 (0.7)	9 (0.7)	0 (0.0)	0.022	21 (0.5)	0.395
HTN	164 (58.2)	1,126 (63.8)	867 (66.6)	604 (67.0)	0.018	2,597 (65.5)	0.014
DM	61 (21.6)	460 (26.1)	368 (28.3)	276 (30.6)	0.009	1,104 (27.8)	0.027
Dyslipidemia	62 (22.0)	517 (29.3)	340 (26.1)	253 (28.1)	0.036	1,110 (28.0)	0.032
Recent smoking	84 (29.8)	537 (30.4)	390 (30.0)	265 (29.4)	0.957	1,192 (30.1)	0.947
Atrial fibrillation	97 (34.4)	578 (32.8)	380 (29.2)	268 (29.7)	0.084	1,226 (30.9)	0.231
Prior antiplatelet	82 (29.1)	493 (27.9)	377 (29.0)	232 (25.7)	0.389	1,102 (27.8)	0.631
Prior anticoagulation	11 (3.9)	53 (3.0)	57 (4.4)	20 (2.2)	0.032	130 (3.3)	0.604
Prior antihypertensive	131 (46.5)	837 (47.4)	686 (52.7)	457 (50.7)	0.019	1,980 (49.9)	0.268
Prior statin	54 (19.1)	317 (18.0)	210 (16.1)	162 (18.0)	0.456	689 (17.4)	0.465
Prior antidiabetic	48 (17.0)	328 (18.6)	261 (20.1)	196 (21.8)	0.161	785 (19.8)	0.278
Multiterritory lesions	33 (11.7)	225 (12.8)	192 (14.8)	148 (16.4)	0.037	565 (14.2)	0.250
IV-tPA dose					0.043		0.470
0.6 mg/kg	57 (20.2)	407 (23.1)	281 (21.6)	237 (26.3)		925 (23.3)	
0.9 mg/kg	225 (79.8)	1,357 (76.9)	1,020 (78.4)	664 (73.7)		3,041 (76.7)	
Laboratory finding							
WBC (10^3/μL)	8.05±2.76	8.03±2.78	8.32±3.01	8.67±3.23	<0.001	8.27±2.97	0.220
Hb (g/dL)	13.8±1.9	13.9±1.9	13.7±1.9	13.6±1.9	0.003	13.8±1.9	0.611
Platelets (10^3/μL)	220.4±67.1	224.2±68.3	227.4±67.6	224.0±69.2	0.335	225.2±68.3	0.252
Glucose (mg/dL)	132.3±44.7	138.0±51.3	144.8±60.0	147.5±58.8	<0.001	142.4±56.1	<0.002
LDL-C (mg/dL)	106.1±34.3	110.1±35.1	110.1±36.5	108.4±35.9	0.234	109.7±35.7	0.103
PT (INR)	1.04±0.17	1.03±0.14	1.04±0.29	1.03±0.13	0.266	1.03±0.20	0.496
SBP (mm Hg)	147.0±25.4	152.6±28.5	149.8±27.3	148.8±26.9	<0.001	150.8±27.8	0.015

Values are presented as mean±standard deviation, number (%), or median (interquartile range). *P*-values are from Pearson's chi-square test, Fisher's exact test, analysis of variance (ANOVA), or a Kruskal-Wallis test, where appropriate.

IV-tPA, intravenous tissue plasminogen activator; OTT, onset-to-treatment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index; DTT, door-to-treatment; OTD, onset-to-door; TOAST, Trial of Org 10172 in Acute Stroke Treatment; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; OE, other etiology; UD, undetermined etiology; TIA, transient ischemic attack; CAD, coronary artery disease; PAD, peripheral artery disease; HTN, hypertension; DM, diabetes mellitus; WBC, white blood cell; Hb, hemoglobin; LDL-C, low density lipoprotein cholesterol; PT, prothrombin time; INR, international normalization ratio; SBP, systolic blood pressure.

https://doi.org/10.5853/jos.2020.04658

Supplementary Table 2. Association between OTT time and functional and safety outcomes

Variable	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
mRS 0–1 at 3 months				
Binary				
OTT ≤60 min	1.24 (0.97–1.58)	0.085	1.24 (0.94–1.63)	0.123
OTT 61–270 min	Reference		Reference	
Categorical				
OTT ≤60 min	1.43 (1.09–1.87)	0.009	1.42 (1.05–1.92)	0.025
OTT 61–120 min	1.30 (1.11–1.53)	0.002	1.25 (1.04–1.51)	0.016
OTT 121–180 min	1.09 (0.92–1.30)	0.334	1.09 (0.90–1.33)	0.364
OTT 181–270 min	Reference		Reference	
Continuous				
OTT, continuous, for every 30-min increase	0.94 (0.91–0.97)	<0.0001	0.94 (0.91–0.98)	0.001
Death				
Binary				
OTT ≤60 min	0.87 (0.56–1.36)	0.547	0.81 (0.50–1.30)	0.376
OTT 61–270 min	Reference		Reference	
Categorical				
OTT ≤60 min	0.74 (0.46–1.18)	0.207	0.67 (0.40–1.13)	0.136
OTT 61–120 min	0.75 (0.58–0.99)	0.040	0.77 (0.57–1.04)	0.090
OTT 121-180 min	0.86 (0.65–1.14)	0.285	0.82 (0.60–1.12)	0.216
OTT 181–270 min	Reference		Reference	
Continuous				
OTT, continuous, for every 30-min increase	1.07 (1.01–1.12)	0.018	1.07 (1.01–1.13)	0.030
SICH				
Binary				
OTT ≤60 min	0.87 (0.35–2.15)	0.757	0.87 (0.35–2.18)	0.761
OTT 61–270 min	Reference		Reference	
Categorical				
OTT ≤60 min	1.23 (0.44–3.49)	0.693	1.22 (0.42–3.48)	0.716
OTT 61–120 min	1.63 (0.87–3.05)	0.130	1.55 (0.82–2.93)	0.180
OTT 121–180 min	1.45 (0.74–2.82)	0.277	1.47 (0.75–2.88)	0.267
OTT 181–270 min	Reference		Reference	
Continuous				
OTT, continuous, for every 30-min increase	0.91 (0.81–1.02)	0.101	0.92 (0.81–1.03)	0.144

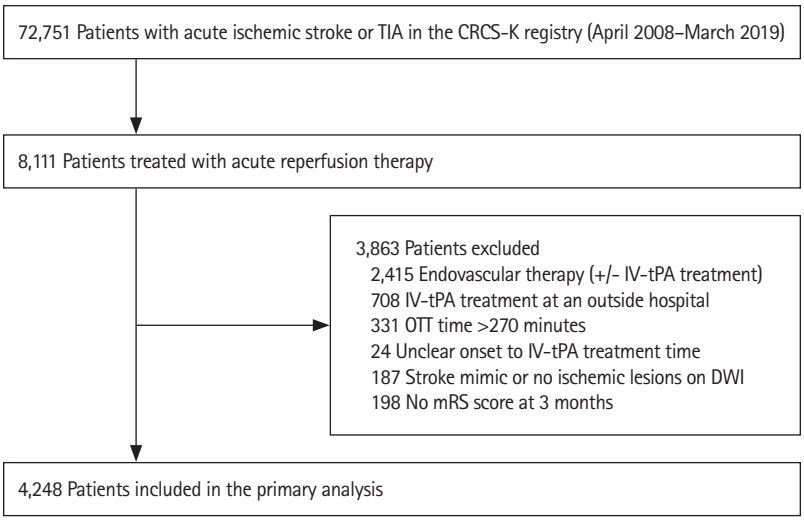
Adjustment variables: age, male sex, initial National Institutes of Health Stroke Scale score, history of stroke, hypertension, diabetes mellitus, atrial fibrillation, prior statin use, systolic blood pressure, glucose, tissue plasminogen activator dose, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.
OTT, onset-to-treatment; OR, odds ratio; CI, confidence interval; mRS, modified Rankin Scale; SICH, symptomatic intracerebral hemorrhage.

Supplementary Table 3. Annual trend in time-to-treatment variables

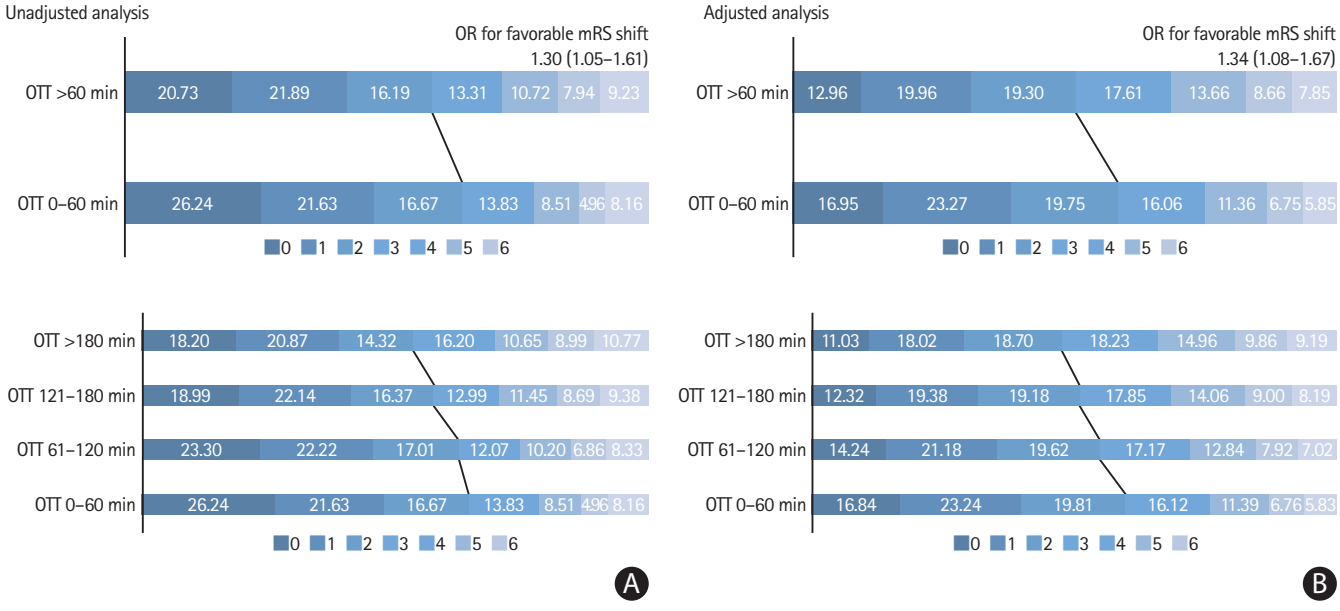
Year	No.	OTT (min)	DTT (min)	OTD (min)	DTT ≤30 min (%)	OTT ≤60 min (%)	OTD ≤30 min (%)
2009	102	126.5 (90 to 160)	53.5 (40 to 75)	58.5 (30 to 107.8)	12.75	6.86	24.51
2010	113	114 (85 to 150.5)	48 (35 to 67)	60 (36.5 to 90)	15.04	4.42	15.93
2011	349	120 (91 to 156)	42 (34 to 54)	73 (45 to 110)	17.19	2.58	11.17
2012	417	130 (90 to 175)	41 (31 to 52)	84 (45 to 131)	22.30	4.32	13.43
2013	464	125 (88 to 175)	35 (27 to 46)	81.5 (49 to 133.8)	35.99	5.39	11.85
2014	565	124 (85 to 180)	36 (28 to 48)	76 (40.5 to 140)	33.98	8.32	15.22
2015	509	125 (82 to 174)	36 (26 to 48)	79 (43 to 133)	36.54	6.68	10.81
2016	554	128 (82.8 to 187)	36 (25 to 53)	77 (44 to 137.5)	35.20	8.84	9.93
2017	504	122 (86 to 181.5)	40 (29 to 56)	70 (40 to 124)	28.17	8.73	13.49
2018	477	121 (85 to 170)	38 (29 to 53)	70 (40 to 124)	28.51	6.71	12.16
Mar 2019	125	120 (85.5 to 178)	37 (27 to 49)	76 (46 to 124)	36.80	8.80	10.40
Per 1 year (95% CI)		0.19 (−1.12 to 1.50)	−0.53 (−1.58 to 0.53)	0.67 (−0.42 to 1.77)	NA	NA	NA
OR (per 1 yr, 95% CI)		NA	NA	NA	1.09 (0.96 to 1.24)	1.12 (1.03 to 1.21)	0.97 (0.93 to 1.01)
P		0.774	0.327	0.229	0.171	0.005	0.192

Values are presented as median (interquartile range). *P*-value by generalized estimating equations linear regression or logistic regression models adjusted for age, sex and initial National Institutes of Health Stroke Scale scores.
OTT, onset-to-treatment; DTT, door-to-treatment; OTD, onset-to-door; CI, confidence interval; NA, not applicable; OR, odds ratio.

https://doi.org/10.5853/jos.2020.04658



Supplementary Figure 1. Selection of the study population. TIA, transient ischemic attack; CRCS-K, Clinical Research Collaboration for Stroke in Korea; IV-tPA, intravenous tissue plasminogen activator; OTT, onset-to-treatment; DWI, diffusion weighted imaging; mRS, modified Rankin Scale.



Supplementary Figure 2. Unadjusted (A) and adjusted (B) modified Rankin Scale (mRS) score distributions according to onset-to-treatment (OTT) time. OR, odds ratio.