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.

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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.

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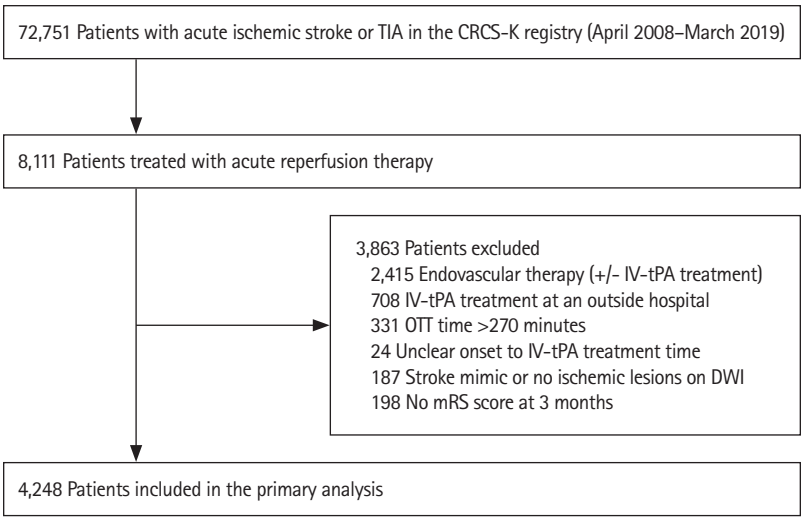
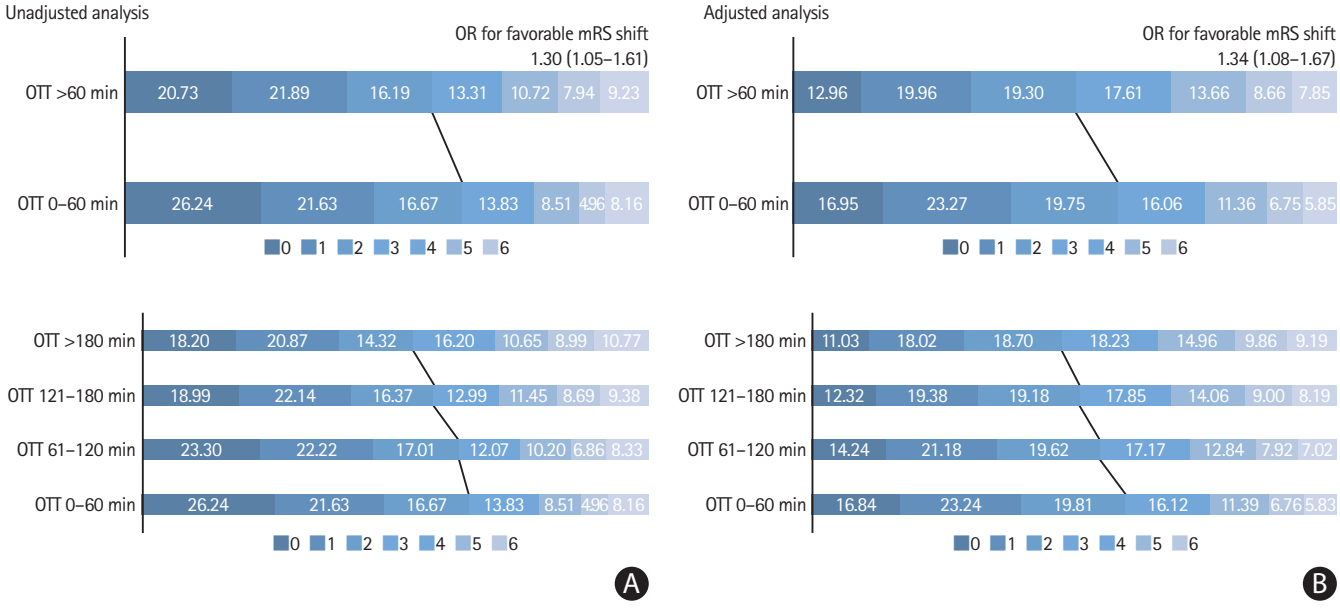


Supplementary Figure 1. Selection of the study population. TIA, transient ischemic attack; CRCS-K, Clinical Research Collaboration for Stroke in Korea; IV-tPA, intravenous tissue plasminogen activator; OTT, onset-to-treatment; DWI, diffusion weighted imaging; mRS, modified Rankin Scale.



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