

# National Trends in Clinical Outcomes of Endovascular Therapy for Ischemic Stroke in South Korea between 2008 and 2016

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Dear Sir:

The advent of mechanical thrombectomy (MT) in 2015 drastically changed the treatment of acute stroke.<sup>1</sup> The corresponding guidelines were revised in 2019 to broaden the scope of MT within 24 hours of symptom onset.<sup>2</sup> In previous studies, MT have improved the prognoses of patients in real-world clinical settings.<sup>3,4</sup> Using nationwide representative data, this study aimed to evaluate the national trends in clinical outcomes of patients treated with endovascular therapy (ET) in South Korea.

From the Korean National Health Insurance Service database,<sup>5</sup> we extracted the claims data of patients aged >45 years who were hospitalized due to cerebral infarction (International Classification of Diseases, 10th revision, code: I63) and underwent ET (based on the registered procedure codes) between 2007 and 2017. We categorized the analysis period as follows: the "non-advanced MT period (January 2008 to December 2010)," when stent retrievers were rarely used; "transitional period (January 2011 to July 2014)," when stent retrievers were used off-label and were not reimbursed; and the "MT period (August 2014 to December 2016)," when the insurance claims data verified the frequency of stent retriever use. We categorized the status of discharge to home as a good outcome and statuses of cerebral hemorrhage, disability, and death as poor outcomes. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to perform statistical analysis. Methods are provided in detail in the Supplementary methods. This study was approved by the Institutional Review Board of the National Health

Insurance Service Ilsan Hospital (NHIMC 2019-01-006).

Between 2008 and 2016, a total of 12,501 patients with acute ischemic stroke were treated with ET. In 2015, ET was administered at a higher rate than that in the previous year. During the study period, the annual rate of discharge to home significantly increased, whereas the rates of cerebral hemorrhage, disability, and death significantly decreased ( $P < 0.0001$ ) (Figure 1). The rate of home discharge was 35.8% in 2008 and 43.8% in 2016. The 3-month mortality rate was 27.2% in 2008 and 19.7% in 2016. The ratio of patients receiving surgery for



**Figure 1.** Annual trends among patients treated for ischemic stroke with endovascular therapy (ET) from 2008 to 2016 and their outcomes. All  $P$ -values were  $< 0.0001$  on the Cochran-Armitage trend test.

cerebral hemorrhage within 30 days gradually decreased from 6.8% in 2008 to 1.8% in 2016. Furthermore, the rate of disability was 36.8% in 2008 and 21.7% in 2016.

A period-based analysis revealed that the patients' average age and the prevalence of risk factors increased gradually during the study period. The highest proportion of comorbidities and Charlson comorbidity index was noted in the MT period. The rate of home discharge increased and the mortality rates decreased continuously from the non-advanced MT period to the MT period. Additionally, the ratio of the patients receiving surgery for cerebral hemorrhage after ET decreased during the study period. The rate of disability after ischemic stroke also showed a significant decrease from the non-advanced MT period to the MT period (Table 1). The 1-year survival rate tended to increase from the non-advanced MT period to the MT period ( $P<0.0001$ ) (Figure 2). After adjusting for age, sex, comorbidities,

and use of tissue plasminogen activator, the risk of death and disability were significantly lower in the MT and transitional periods than in the non-advanced MT period. Logistic regression analysis adjusted for the same covariates revealed the MT period was an independent predictor of home discharge (Supplementary Table 1).

In agreement with other studies,<sup>3,4</sup> our analysis of the nationwide data showed that the patients treated with ET had better outcomes in the MT period than in the non-advanced MT period. Over time, the baseline prognostic characteristics, reflected by age and comorbidities, got worse; however, the outcomes of the patients generally improved; this was supported by the annual trend analyses (Supplementary Table 2).

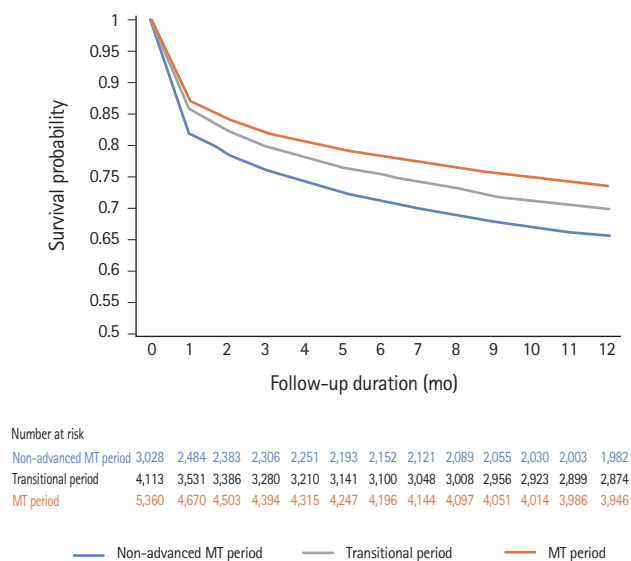
In this study, the rates of mortality, disability, and cerebral hemorrhage decreased with the increased application of ET. The 3-month mortality rate in the MT period observed in the

**Table 1.** Baseline characteristics and outcomes of patients according to the period of endovascular therapy adoption

Characteristic	Non-advanced MT period	Transitional period	MT period	P	Standardized difference (%)		
					Non-advanced MT period and transitional period	Non-advanced MT period and MT period	Transitional period and MT period
Number	3,028	4,113	5,360				
Male sex	1,691 (55.8)	2,246 (54.6)	2,968 (55.4)	0.5619	2.490	0.951	-1.539
Age (yr)	69.00±10.70	70.97±10.81	71.08±11.02	<0.0001	-18.294	-19.158	-1.032
<60	630 (20.8)	706 (17.2)	931 (17.4)	<0.0001	9.293	8.753	-0.541
60–69	785 (25.9)	938 (22.8)	1,251 (23.3)		7.270	6.003	-1.267
70–79	1,124 (37.1)	1,519 (36.9)	1,850 (34.5)		0.390	5.436	5.045
≥80	489 (16.1)	950 (23.1)	1,328 (24.8)		-17.563	-21.507	-3.935
Hypertension	2,119 (70.0)	3,192 (77.6)	4,125 (77.0)	<0.0001	-17.410	-15.857	1.548
Diabetes mellitus	975 (32.2)	1,807 (43.9)	2,574 (48.0)	<0.0001	-24.346	-32.713	-8.211
Dyslipidemia	1,147 (37.9)	2,400 (58.4)	3,648 (68.1)	<0.0001	-41.861	-63.435	-20.234
Atrial fibrillation	1,411 (46.6)	2,137 (52.0)	2,861 (53.4)	<0.0001	-10.734	-13.588	-2.844
Ischemic heart disease	798 (26.4)	1,465 (35.6)	2,007 (37.4)	<0.0001	-20.136	-23.964	-3.791
Chronic kidney disease	202 (6.7)	373 (9.1)	427 (8.0)	0.0011	-8.913	-4.975	3.950
CCI >5	1,255 (41.4)	2,410 (58.6)	3,427 (63.9)	<0.0001	-34.812	-46.233	-10.982
Intravenous tPA	1,025 (33.9)	1,283 (31.2)	2,032 (37.9)	<0.0001	5.674	-8.472	-14.160
3-month mortality	777 (25.7)	903 (22.0)	1,045 (19.5)	<0.0001	8.709	14.784	6.068
1-year mortality	1,046 (34.5)	1,239 (30.1)	1,414 (26.4)	<0.0001	9.461	17.808	8.322
Cerebral hemorrhage (I61)	195 (6.4)	152 (3.7)	133 (2.5)	<0.0001	12.536	19.264	7.023
Cerebral hemorrhage (operation)	149 (4.9)	112 (2.7)	102 (1.9)	<0.0001	11.481	16.681	5.458
Disability	1,016 (33.6)	1,092 (26.5)	1,254 (23.4)	<0.0001	15.320	22.653	7.292
Home discharge without events	1,086 (35.9)	1,632 (39.7)	2,233 (41.7)	<0.0001	-7.873	-11.916	-4.034
Home discharge and re-admission within 30 days	48 (1.6)	71 (1.7)	67 (1.3)	0.1938	-1.105	2.836	3.934
Home discharge and death within 30 days	113 (3.7)	99 (2.4)	109 (2.0)	<0.0001	7.686	10.163	2.535

Values are presented as number (%) or mean±standard deviation.

MT, mechanical thrombectomy; CCI, Charlson comorbidity index; tPA, tissue plasminogen activator.



**Figure 2.** Kaplan-Meier curve of 1-year mortality in the patients treated for ischemic stroke by the period of endovascular therapy adoption ( $P < 0.0001$ ). MT, mechanical thrombectomy.

current study was higher than that reported in a meta-analysis of pivotal clinical trials,<sup>6</sup> but it was lower than that reported in a real-world data study.<sup>7</sup> The 3-month mortality rate during the transitional period was similar to that reported by a study performed around the time when stent retrievers were introduced.<sup>8</sup> We could not verify the clinical data from this claim data; therefore, we used disability registration data following cerebral injury rather than modified Rankin Scale (mRS) to evaluate patient prognosis. The ratio of patients with an mRS of 3–5 (vs. 0–2) at 3-months in the meta-analysis of clinical studies and real-world data was higher than the rate of patients with cerebral injury-related disability among the patients in the national database used in our study.<sup>6,7</sup> This difference could possibly be because some patients with an mRS of 3–5 at 3 months would have returned to their daily lives after rehabilitation. When patients survive with a disability after a stroke event, their direct medical costs and indirect social costs increase.<sup>9</sup> Therefore, verifying decreases in the number of such disabled patients is meaningful.

This study has several limitations. We used insurance claims data rather than well-designed clinical trial or prospective registry data. Therefore, we were unable to adjust for detailed and important prognostic factors such as initial National Institutes of Health Stroke Scale scores, occlusion sites, recanalization status, and interval from symptom onset to recanalization. In addition, we were unable to verify the precise number of patients who received ET in the period when solitaire stents, the most

common ET instrument, were only used off-label or when the solitaire stents were not covered by insurance. Improved outcomes of patients treated with ET in the transitional period compared to those of patients treated with ET in the non-advanced MT period is likely attributed to the increasing use of MT. However, we had no data on the proportion of patients treated with MT during the transition period and our interpretation is not supported by formal analysis.

In conclusion, our analysis of nationwide insurance data verified that the rates of mortality and disability associated with stroke have decreased with the increasingly widespread adoption of stent retrievers.

## Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2020.01928>.

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**Supplementary Table 1.** HRs and ORs for death, disability, and home discharge in patients between the MT, transitional period and the non-advanced MT period

Variable	Death			Disability			Home discharge		
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P
Non-advanced MT period	1	1	1	1	1	1	1	1	1
Transitional period	0.908 (0.852-0.968)	0.816 (0.765-0.871)	<0.0001	0.677 (0.619-0.741)	0.689 (0.629-0.755)	<0.0001	1.178 (1.069-1.298)	1.214 (1.100-1.340)	<0.0001
MT period	0.762 (0.711-0.816)	0.693 (0.645-0.744)	<0.0001	0.744 (0.681-0.812)	0.750 (0.684-0.822)	<0.0001	1.273 (1.161-1.395)	1.302 (1.183-1.434)	<0.0001

Adjusted HR and OR for age, sex, comorbidities, and use of tissue plasminogen activator. HR, hazard ratio; OR, odds ratio; MT, mechanical thrombectomy; CI, confidence interval.

**Supplementary Table 2.** Baseline characteristics and outcomes of patients according to the calendar year

Characteristic	2008	2009	2010	2011	2012	2013	2014	2015	2016	Cochran-Armitage trend test, <i>P</i>
Number	869	1,000	1,159	1,356	992	1,093	1,359	2,059	2,614	
Male sex	502 (57.8)	556 (55.6)	633 (54.6)	760 (56.0)	545 (54.9)	590 (54.0)	724 (53.3)	1,115 (54.2)	1,480 (56.6)	0.5631
Age (yr)	68.29±10.88	69.37±10.54	69.21±10.68	69.84±10.61	70.69±10.78	71.77±11.02	71.72±10.78	70.82±10.99	71.29±11.08	
<60	202 (23.2)	193 (19.3)	235 (20.3)	252 (18.6)	181 (18.2)	179 (16.4)	210 (15.5)	360 (17.5)	455 (17.4)	<0.0001
60–69	227 (26.1)	280 (28.0)	278 (24.0)	344 (25.4)	217 (21.9)	231 (21.1)	295 (21.7)	491 (23.8)	611 (23.4)	0.0043
70–79	305 (35.1)	352 (35.2)	467 (40.3)	505 (37.2)	376 (37.9)	387 (35.4)	513 (37.7)	724 (35.2)	864 (33.1)	0.0084
≥80	135 (15.5)	175 (17.5)	179 (15.4)	255 (18.8)	218 (22.0)	296 (27.1)	341 (25.1)	484 (23.5)	684 (26.2)	<0.0001
Hypertension	554 (63.8)	705 (70.5)	860 (74.2)	1,026 (75.7)	776 (78.2)	855 (78.2)	1,084 (80.0)	1,562 (75.9)	2,014 (77.0)	<0.0001
Diabetes mellitus	251 (28.9)	311 (31.1)	413 (35.6)	559 (41.2)	433 (43.6)	508 (46.5)	633 (46.6)	956 (46.4)	1,292 (49.4)	<0.0001
Dyslipidemia	272 (31.3)	373 (37.3)	502 (43.3)	701 (51.8)	565 (57.0)	677 (61.9)	914 (67.3)	1,364 (66.2)	1,827 (69.9)	<0.0001
Atrial fibrillation	390 (44.9)	466 (46.6)	555 (47.9)	689 (50.8)	511 (51.5)	558 (51.1)	736 (54.2)	1,119 (54.3)	1,385 (53.0)	<0.0001
Ischemic heart disease	165 (19.0)	280 (28.0)	353 (30.5)	436 (32.2)	364 (36.7)	400 (36.6)	516 (38.0)	766 (37.2)	990 (37.9)	<0.0001
Chronic kidney disease	61 (7.0)	69 (6.9)	72 (6.2)	108 (8.0)	80 (8.1)	107 (9.8)	133 (9.8)	160 (7.8)	212 (8.1)	0.0312
CCI >5	269 (31.0)	424 (42.4)	562 (48.5)	728 (53.7)	564 (56.9)	681 (62.3)	864 (63.6)	1,267 (61.5)	1,733 (66.3)	<0.0001
Intravenous tPA	290 (33.3)	337 (33.7)	398 (34.3)	426 (31.4)	313 (31.6)	318 (29.1)	497 (36.6)	751 (36.5)	1,010 (38.6)	<0.0001
3-month mortality	236 (27.2)	273 (27.3)	268 (23.1)	306 (22.6)	219 (22.1)	232 (21.2)	287 (21.1)	389 (18.9)	515 (19.7)	<0.0001
1-year mortality	316 (36.4)	365 (36.5)	365 (31.5)	414 (30.5)	295 (29.7)	322 (29.5)	393 (28.9)	534 (25.9)	695 (26.6)	<0.0001
Cerebral hemorrhage (I61)	77 (8.9)	65 (6.5)	55 (4.7)	64 (4.7)	35 (3.5)	36 (3.3)	38 (2.8)	44 (2.1)	66 (2.5)	<0.0001
Cerebral hemorrhage (operation)	59 (6.8)	36 (3.6)	54 (4.7)	48 (3.5)	25 (2.5)	23 (2.3)	30 (2.2)	42 (2.0)	46 (1.8)	<0.0001
Disability	320 (36.8)	323 (32.3)	373 (32.2)	415 (30.6)	253 (25.5)	253 (23.1)	359 (26.4)	500 (24.3)	566 (21.7)	<0.0001
Home discharge without event	311 (35.8)	357 (35.7)	418 (36.1)	537 (39.6)	394 (39.7)	424 (38.8)	541 (39.8)	825 (40.1)	1,144 (43.8)	<0.0001
Home discharge and re-admission within 30 days	14 (1.6)	18 (1.8)	16 (1.4)	23 (1.7)	15 (1.5)	22 (2.0)	16 (1.2)	29 (1.4)	33 (1.3)	0.2068
Home discharge and death within 30 days	50 (5.8)	42 (4.2)	21 (1.8)	38 (2.8)	21 (2.1)	24 (2.2)	36 (2.6)	35 (1.7)	54 (2.1)	<0.0001

Values are presented as number (%) or mean±standard deviation. CCI, Charlson comorbidity index; tPA, tissue plasminogen activator.

## Supplementary methods

### Study population

We used data from the Korean National Health Insurance database, which has data on 97% of the South Korean population. We extracted all insurance claims data of patients aged >45 years who were hospitalized due to cerebral infarction (International Classification of Diseases, 10th revision, code [ICD-10 code]: I63) as the main or first subdiagnosis between 2007 and 2017. After considering the washout and follow-up periods, we excluded data from the years 2007 and 2017. Further, we sorted the claims data by procedure codes related to thrombectomy and determined whether a tissue plasminogen activator (tPA) was used during thrombectomy in these patients by referring to the Anatomical Therapeutic Chemical Classification System code B01AD02 or product code 653500661.

We classified the patients based on tPA use and the period when endovascular therapy (ET) was performed. It was estimated that off-label stent retrievers were used in South Korea between October and December of 2010. Even though its usage was officially approved, stent retrievers were not reimbursed by the South Korean National Health Insurance between May 2013 and July 2014. Therefore, we categorized the period when stent retrievers were rarely used as the "non-advanced MT period (January 2008 to December 2012)"; when we could not precisely identify stent retriever usage as the "transitional period (January 2011 to July 2014)"; and when the insurance claim data verified the frequency of stent retriever use as the "MT period (August 2014 to December 2016)."

This study was approved by the Institutional Review Board of the National Health Insurance Service Ilsan Hospital (NHIMC 2019-01-006).

### Outcome and covariates

Good outcomes were defined as discharge of patients to their homes after 30 days without significant issues such as death or rehospitalization. To screen patients with good outcomes, we tracked the insurance claims of patients who were discharged home after hospitalization for stroke treatment. To increase the reliability of good outcomes, we excluded patients who had died within 30 days of discharge and those who had claimed rehospitalization under either ICD-10 code I63 or I61

within 30 days of discharge because their prognosis was expected to be poor even if they experienced recurrence or were rehospitalized for rehabilitation.

Poor outcomes were defined as cerebral hemorrhage after the procedure, significant disability, and death. To identify the incidence rate of cerebral hemorrhage, we screened patients with insurance claims of ICD-10 code I61 as the main diagnosis, as the first subdiagnosis, or with a procedure code related to cerebral hemorrhage within 30 days of ET. The procedure codes used for screening were N0322 (burr Hole), N0333 (craniectomy), and S4756/S4622 (hematoma removal). We tracked deaths within 3 months and 1 year of ET using mortality data. In South Korea, the registration of disability is possible when at least 6 months have passed from the time of the stroke event, permitting patients to register for the cerebral injury disability. We further excluded patients who received ET in 2017 as we could not track their deaths within 1 year or their status of disability registration for cerebral injury from the selected data. Consequently, we analyzed patients and outcome variables by year and then conducted a comparison analysis based on the non-advanced MT, transitional, and MT periods.

We identified the comorbidities (hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation) that could increase the risk of stroke and, thus, affect the prognosis and the risk factors of patients from the insurance claims data prior to ET treatment and during hospitalization for ET. We analyzed the Charlson comorbidity index of patients to verify the influence of comorbidities on death.

### Statistical analysis

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for data analysis. To compare descriptive statistics and the frequency of risk factors, one-way analysis of variance and the chi-square test were used. To compare the distribution of baseline covariates between the analysis periods, we used the standardized differences test. To confirm the difference in the inclinations of the outcome variables by year, we performed the Cochran-Armitage trend test. We performed a time-dependent Cox proportional hazard regression analysis to identify the risk factors for death and cerebral injury disability. To identify the factors related to home discharge, multiple logistic regression analysis was used. *P*-values of <0.05 for the two-sided tests were considered to indicate statistical significance.