

ORIGINAL RESEARCH

Temporal Trends in Stroke Management and Outcomes Between 2011 and 2020 in South Korea: Results From a Nationwide Multicenter Registry

Tai Hwan Park , MD, PhD; Keun-Sik Hong , MD, PhD; Yong-Jin Cho , MD, PhD; Wi-Sun Ryu , MD, PhD; Dong-Eog Kim, MD, PhD; Man-Seok Park , MD, PhD; Kang-Ho Choi , MD, PhD; Joon-Tae Kim , MD, PhD; Jihoon Kang , MD, PhD; Beom-Joon Kim , MD, PhD; Moon-Ku Han , MD, PhD; Jun Lee , MD, PhD; Jae-Kwan Cha , MD, PhD; Dae-Hyun Kim , MD, PhD; Jae Guk Kim , MD, PhD; Soo Joo Lee , MD, PhD; Jee-Hyun Kwon , MD, PhD; Wook-Joo Kim , MD, PhD; Dong-Ick Shin , MD, PhD; Kyu Sun Yum , MD, PhD; Sung Il Sohn , MD, PhD; Jeong-Ho Hong , MD, PhD; Jay Chol Choi , MD, PhD; Byung-Chul Lee , MD, PhD; Kyung-Ho Yu , MD, PhD; Mi-Sun Oh , MD, PhD; Jong-Moo Park , MD, PhD; Kyusik Kang , MD, PhD; Kyungbok Lee , MD, PhD; Sang-Hwa Lee, MD, PhD; Hae-Bong Jeong , MD; Kwang-Yeol Park , MD, PhD; Ji Sung Lee , PhD; Juneyoung Lee , PhD; Philip B. Gorelick , MD, MPH; Hee-Joon Bae , MD, PhD

BACKGROUND: This study aims to evaluate temporal trends of advanced treatments and related clinical outcomes of ischemic stroke through a decade-long trend analysis, using data from a comprehensive, national, multicenter registry. We also seek to identify areas in need of improvement.

METHODS AND RESULTS: This analysis involved patients with ischemic stroke or transient ischemic attack registered prospectively in the CRCS-K-NIH (Clinical Research Center for Stroke in Korea–National Institute of Health) registry between 2011 and 2020. We examined temporal trends in risk factors, pathogenetic subtypes, acute management strategies, and outcomes for up to 1 year following a stroke. Generalized linear mixed models were used to account for center clustering. The average age of 77 662 patients increased 2.2 years in men and 2.4 years in women over the 10-year follow-up. Notably, in-hospital neurological deterioration, 3-month and 1-year mortality rate, and cumulative incidence of recurrent stroke within 1-year decreased over time after adjustments for age, sex, and initial stroke severity ($P<0.01$). However, functional outcomes at 3 months and 1 year remained unchanged. Endovascular thrombectomy increased from 5.4% in 2011 to 10.6% in 2020. Use of anticoagulants for atrial fibrillation, dual antiplatelet therapy, statins, and stroke unit care also increased. Contrarily, the rate of intravenous thrombolysis showed a slight decline.

CONCLUSIONS: This study points to a reduction in death and risk of recurrent stroke over the past decade, paralleling enhancement in acute and preventive stroke management. Nevertheless, the decline in the use of intravenous thrombolysis and the lack of improvement in functional outcomes following stroke are concerning trends that warrant thorough investigation.

Key Words: advanced treatments ■ clinical outcomes ■ ischemic stroke ■ temporal trends

Correspondence to: Hee-Joon Bae, MD, PhD, FAHA, Department of Neurology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Republic of Korea. Email: braindoc@snu.ac.kr

This manuscript was sent to Kori S. Zachrison, MD, MSc, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Preprint posted on MedRxiv, March 2, 2024. doi: <https://doi.org/10.1101/2024.02.29.24303345>.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.035218>

For Sources of Funding and Disclosures, see page 11.

© 2025 The Author(s). Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](#) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This study shows that the increased use of advanced treatments like endovascular thrombectomy and use of anticoagulants for atrial fibrillation, dual antiplatelet therapy, and statins has coincided with decreased in-hospital neurological deterioration, death, and recurrent stroke rates over the past decade in South Korea.
- Functional outcomes at 3 months and 1 year following a stroke remained unchanged, and intravenous thrombolysis rates slightly declined during the study period.

What Are the Clinical Implications?

- Further study is needed to explore barriers to optimal stroke treatment delivery to address the stagnation in functional outcomes and thrombolysis rates.

Nonstandard Abbreviations and Acronyms

CRCS-K-NIH	Clinical Research Collaboration for Stroke in Korea–National Institute of Health
EVT	endovascular thrombectomy
IVT	intravenous thrombolysis
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NOAC	novel oral anticoagulant

Over the past decade, ischemic stroke treatment has seen significant advancements with the introduction of stent retrievers for endovascular thrombectomy (EVT),¹ novel oral anticoagulants (NOACs) for atrial fibrillation,^{2–4} dual antiplatelet therapy for minor strokes or high-risk transient ischemic attacks (TIAs),^{5,6} and high-dose statins for atherosclerotic stroke prevention.^{7,8} While these treatments have been successfully integrated into clinical practice,^{9,10} their comprehensive impact on clinical outcomes warrants further investigation.

Evaluating these treatments' effectiveness requires examining both stroke recurrence and functional outcomes, as their impacts may vary on the basis of the outcome measured. For example, appropriate anti-thrombotic selection can reduce stroke recurrence,¹¹

and wider use of recanalization therapies and strategies preventing neurological deterioration during hospitalization may enhance functional outcomes.^{1,12}

Despite a reported decline in recurrence and death after stroke,^{13–17} insights into functional outcomes remain limited. Previous studies, like a German population-based study¹⁸ on recurrent stroke risk over 20 years and a comprehensive Japanese study of ischemic stroke cases¹⁹ reporting improving functional outcomes at discharge between 2000 and 2019, have not fully addressed long-term outcomes or the nuances of early treatment and stroke characteristics.

The CRCS-K-NIH (Clinical Research Collaboration for Stroke in Korea–National Institute of Health) registry, initiated in 2008, offers a rich data set on stroke characteristics, treatments, and outcomes.²⁰ Using this registry database, we aim to outline trends in stroke outcomes, including functional outcomes at 3 months and 1 year, major vascular events, and death within the first year. It also seeks to assess trends in acute stroke treatments from 2011 to 2020, aiming to pinpoint areas for quality enhancement.

METHODS

Data Availability

The data analyzed in this study are available from the corresponding author upon reasonable request.

Study Design and Participants

This trend analysis focused on patients with acute ischemic stroke or TIA who were admitted to 18 academic or regional stroke centers in South Korea between January 1, 2011, and December 31, 2020, as identified within the CRCS-K-NIH registry.^{20,21} Some hospitals joined the registry midway through the study period (Table S1). All participating hospitals, including those that joined midstudy, are located in urban areas with populations of $\geq 500\,000$. These hospitals are tertiary or neurology teaching hospitals, each equipped with at least a 4-bed stroke unit. Certification for stroke centers in Korea, initiated by the Korean Stroke Society in 2018, has been achieved by all participating hospitals. The registry operates on a voluntary basis. All consecutive patients with stroke admitted within 7 days of symptom onset and diagnosed by stroke physicians, including both in-hospital and transferred cases, were registered and analyzed in this study. Patients were followed up for a duration of 1 year, with the last follow-up conducted in December 2021. The registry includes demographics, clinical presentation, risk factors, treatments, and quality indicators, collected via a web-based system following predefined protocols. To examine the representativeness of the study subjects, we compared their demographic and

clinical features with those of the national stroke audit data, conducted by the Health Insurance Review and Assessment Service of Korea, covering >200 hospitals across the country.²² We used the audit data collected in 3 periods: 2013 to 2014, 2016, and 2018.

Outcome Catchment

According to predefined protocols of the CRCS-K-NIH registry, we prospectively collected comprehensive data, including in-hospital neurological deterioration, vascular events, functional status, and death. Functional status was rigorously assessed using the modified Rankin Scale (mRS) at multiple follow-up points: specifically, at 3 months and 1 year or during outpatient clinic visits. These assessments were conducted through structured interviews by trained nurse coordinators or by physicians, to optimize consistent and standardized evaluation across all follow-up periods.

Data Quality and Fidelity

Data integrity was maintained through monthly downloads, verification, steering committee reviews, and audits. Since the registry's launch in 2008, the volume of monthly queries, along with feedback provided to each center, has been reported at the monthly steering committee meetings attended by researchers from all participating hospitals. Further details on the quality and fidelity of the data are available in previous literature^{20,21} and on the CRCS-K-NIH website (<http://crs-k.strokedb.or.kr/eng/>).

Study Variables

Evaluated variables included traditional stroke risk factors, prestroke medications, stroke severity (National Institutes of Health Stroke Scale [NIHSS]), stroke onset, onset-to-arrival time, and stroke pathogenetic subtypes. In patients with an unclear stroke onset time, we differentiated between the "first-found-abnormal time" and the "last-known-normal time." Each time point was used distinctly on the basis of its relevance to the specific study analysis.

Diagnostic assessments covered diffusion-weighted imaging, perfusion-weighted imaging, computed tomography/magnetic resonance angiography, echocardiography, and 24-hour Holter monitoring. Treatment variables encompassed intravenous thrombolysis (IVT) and EVT use, door-to-needle and door-to-puncture times, and discharge medications. IVT and EVT rates were calculated regardless of whether patients were transferred to the study hospitals. However, we excluded transferred cases when evaluating time metrics (eg, door-to-needle time, door-to-puncture time), as these metrics might not be attributed to the participating hospitals.

Outcomes measured included neurological deterioration, symptomatic hemorrhagic transformation, hospital stay length, recurrent stroke within 1 year, mRS scores, and death at 3 months and 1 year. In-hospital neurological deterioration was defined as any new neurological symptoms/signs or worsening with an increase in the NIHSS score ≥ 2 occurring during hospitalization within 3 weeks of onset, which excluded hemorrhagic transformation. Symptomatic hemorrhagic transformation was defined as any intracranial hemorrhage associated with a 2-point increase in the NIHSS score. Detailed descriptions of the registry's design and data collection are documented in prior publications.^{20,21}

Ethics Statement

Institutional review boards at all involved centers approved the collection of clinical information in the CRCS-K-NIH registry to monitor and improve the quality and outcomes of stroke care, granting a waiver of informed consent due to data anonymization and minimal participant risk. The institutional review boards also approved this research's specific use of the registry database.

Statistical Analysis

Baseline characteristics, acute treatments, and outcomes were analyzed by calendar year, focusing on the proportions of participants with mild (NIHSS scores <4) and severe strokes (NIHSS scores ≥ 15), onset to arrival time, and the promptness of IVT and EVT administration. Missing data and outliers were handled in a predefined manner: door-to-needle time for patients treated with IVT was analyzed in 8189 subjects, excluding those without data ($n=37$), with door-to-needle times >12 hours ($n=35$), or with negative values due to receiving IVT at referral hospitals ($n=1047$). Door-to-puncture time for patients treated with EVT was analyzed in 5783 patients, excluding those without data ($n=16$), with door-to-puncture times >24 hours ($n=72$), or with negative values due to receiving EVT at referral hospitals ($n=66$). Hospital length of stay was evaluated in 72278 patients with hospitalization durations within 1 SD (2–26 days). The rate of dual antiplatelet therapy at discharge was specifically calculated for 16764 patients with noncardioembolic minor stroke (NIHSS score ≤ 3) or high-risk TIA with a relevant diffusion-weighted imaging lesion.

Calendar year was treated as a continuous variable. Annual trends of the study variables were expressed by the regression coefficient (β), obtained by generalized linear mixed models with a random center effect to control for variations in age, sex, and center in examining baseline characteristics, diagnostic evaluations, and discharge medications. The initial NIHSS

Table. Secular Trends in Baseline Characteristics

Year of admission	Total	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	β	P value*
Number of patients	77 662	5660	5978	6900	7458	7670	8515	8864	8674	9513	8430		
Men, %	58.4	58.0	57.4	58.3	58.1	57.3	58.2	59.7	57.6	59.3	59.8	0.019	<0.01
Women, %	41.6	42.0	42.6	41.7	41.9	42.7	41.8	40.3	42.4	40.7	40.2	-0.019	<0.01
Age, y, mean $\pm$ SD													
Men	65.6 $\pm$ 12.7	64.7 $\pm$ 12.7	65.2 $\pm$ 12.6	64.5 $\pm$ 12.8	65.1 $\pm$ 13.0	65.3 $\pm$ 12.4	65.3 $\pm$ 12.6	65.8 $\pm$ 12.7	65.8 $\pm$ 12.8	66.4 $\pm$ 12.8	66.9 $\pm$ 12.4	0.252	<0.01
Women	71.6 $\pm$ 12.8	70.5 $\pm$ 12.4	70.7 $\pm$ 12.6	70.7 $\pm$ 12.8	71.0 $\pm$ 12.6	71.2 $\pm$ 12.5	71.4 $\pm$ 12.9	71.9 $\pm$ 12.9	72.5 $\pm$ 12.8	72.4 $\pm$ 13.3	72.9 $\pm$ 13.2	0.293	<0.01
Risk factors, %													
Hypertension	65.9	69.3	67.6	66.1	67.0	62.8	64.3	64.0	66.4	65.5	67.5	-0.017	<0.01
Newly diagnosed	9.0	11.2	9.4	9.7	7.7	7.3	8.7	8.7	9.4	9	9.7	-0.009	0.12
Diabetes	32.4	33.4	32.6	32.2	32.5	31.2	31.6	31.5	31.9	32.8	34.6	-0.000	0.87
Newly diagnosed	12.6	13.8	12.1	14.4	10.9	10.3	12.1	13.3	12.3	12.4	14.1	0.004	0.54
Dyslipidemia	30.7	39.1	32.0	27.9	26.0	25.6	30.8	30.5	28.6	32.8	34.6	0.011	<0.01
Newly diagnosed	35.2	56.5	42.8	36.1	33	35.1	36.6	32.5	28.3	30.1	27.7	-0.122	<0.01
Atrial fibrillation	20.0	19.7	20.8	18.9	21.1	21.5	19.5	18.9	20.1	19.6	20.1	-0.018	<0.01
Newly diagnosed	45.9	46.4	38.5	40.9	46.5	46.7	45.6	47.7	45.9	48.4	49.6	0.034	<0.01
History of stroke	20.7	21.3	20.4	20.8	21.1	20.1	20.2	19.9	20.7	21.2	21.7	-0.005	0.15
Current smoking	23.0	25.0	25.4	25.7	24.0	20.5	22.9	23	21.2	21.9	22.4	-0.023	<0.01
Admitted via emergency room, %	89.1	87.7	86.8	87.1	87.6	87.6	88.5	90	90.6	92.2	90.6	0.062	<0.01
Unclear onset, %	40.9	39.1	48.7	48.2	40.4	42.3	37.3	38.8	40.8	41.4	35.6	-0.021	<0.01
From first-found-abnormal time to arrival, h, median (IQR)	7.3 (1.9–32.0)	7.8 (2.2–34.2)	8.0 (2.3–33.2)	7.7 (2.1–34.4)	7.1 (2.0–30.6)	7.6 (2.0–34.6)	6.8 (1.8–31.1)	6.8 (1.9–29.5)	6.8 (1.7–29.9)	7.2 (1.8–31.9)	7.8 (1.9–32.7)	-0.128	0.052
NIHSS at presentation, mean (SD)	5.3 (6.1)	5.4 (6.0)	5.5 (6.2)	5.5 (6.2)	5.7 (6.5)	5.4 (6.3)	5.3 (6.1)	5.2 (5.9)	5.3 (6.1)	5.0 (5.9)	5.1 (5.8)	-0.081	<0.01

The denominator of the newly diagnosed risk factor ratio is the frequency of risk factors. IQR indicates interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

*Adjusted for age and sex with random effects for the center.

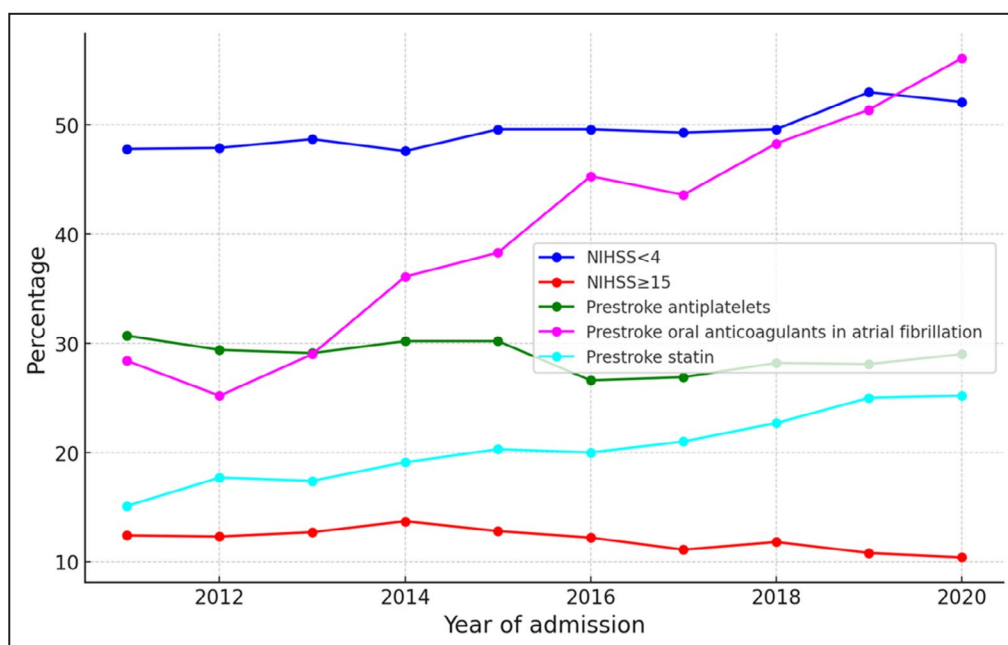


Figure 1. Trends in stroke severity and prestroke medication use (2011–2020).

Mild stroke (NIHSS <4) increased from 47.8% to 53% ($\beta=0.021$, $P<0.01$); severe stroke (NIHSS ≥ 15) decreased from 12.4% to 10.4% ($\beta=-0.034$, $P<0.01$); prestroke antiplatelet use fluctuated slightly and ended at 29% ($\beta=-0.025$, $P<0.01$); prestroke oral anticoagulants use in atrial fibrillation increased from 28.4% to 56.1% ($\beta=0.148$, $P<0.01$); prestroke statin use increased from 15.1% to 25.2% ($\beta=0.059$, $P<0.01$). The regression coefficient (β) of the study variables was obtained by generalized linear mixed models with adjustment for age and sex with random effects for the center (detailed values refer to Table S3). NIHSS indicates National Institutes of Health Stroke Scale.

score was also adjusted in analyses related to acute treatment and outcomes.

Statistical significance was set at a 5% level, with all P values being 2-sided. SAS version 9.4 (SAS Institute, Inc., Cary, NC) was used for statistical analysis.

RESULTS

From 2011 to 2020, 77 662 patients were enrolled in the CRCS-K-NIH registry, with TIA cases constituting 9.3% ($n=7212$). Compared with the national stroke audit cohort, the age distribution and initial NIHSS score ranges of the patients in our study were comparable. Nevertheless, the mean age of our patients (65.6 years in men; 71.6 years in women) was marginally lower, and the mean initial NIHSS score (5.3) was somewhat higher (Table S2 and Figures S1 and S2).

Baseline Characteristics

Over the past decade, the average age of patients increased by 2.2 years for men and 2.4 years for women, with a slight rise in the proportion of male patients (Table). Despite an aging stroke demographic, major modifiable risk factors remained stable. The rate of current smoking showed a slight decreasing trend, and new dyslipidemia diagnoses significantly decreased

from 56.5% in 2011 to 27.7% in 2020 ($P<0.01$). Among patients diagnosed with atrial fibrillation, the rate of oral anticoagulant use before stroke increased significantly from 28.4% in 2011 to 56.1% in 2020. Statin use before stroke also rose steadily, with 25.2% of patients using statins in 2020. Stroke severity at presentation decreased, with the mean initial NIHSS score dropping from 6.0 to 5.4. The instances of mild stroke (NIHSS <4) increased, while severe strokes (NIHSS ≥ 15) declined (Figure 1 and Table S3). Emergency room admissions increased slightly, with no meaningful change in onset-to-arrival times. Large-artery atherosclerosis remained the leading ischemic stroke subtype, with slight shifts in subtype proportions over time (Figure 2 and Table S4).

Stroke Management

Among 70 450 patients excluding TIA, EVT usage increased from 5.4% in 2011 to 10.6% in 2020, while IVT rates declined (Figure 3). These trends were consistent across different patient groups, including those with the cardioembolism subtype, patients using oral anticoagulants before stroke, patients aged >80 years, and those arriving at the hospital within different time windows (<4.5 hours, 4.5–24 hours from the last-known-normal time, or with unclear onset; Figure 4).

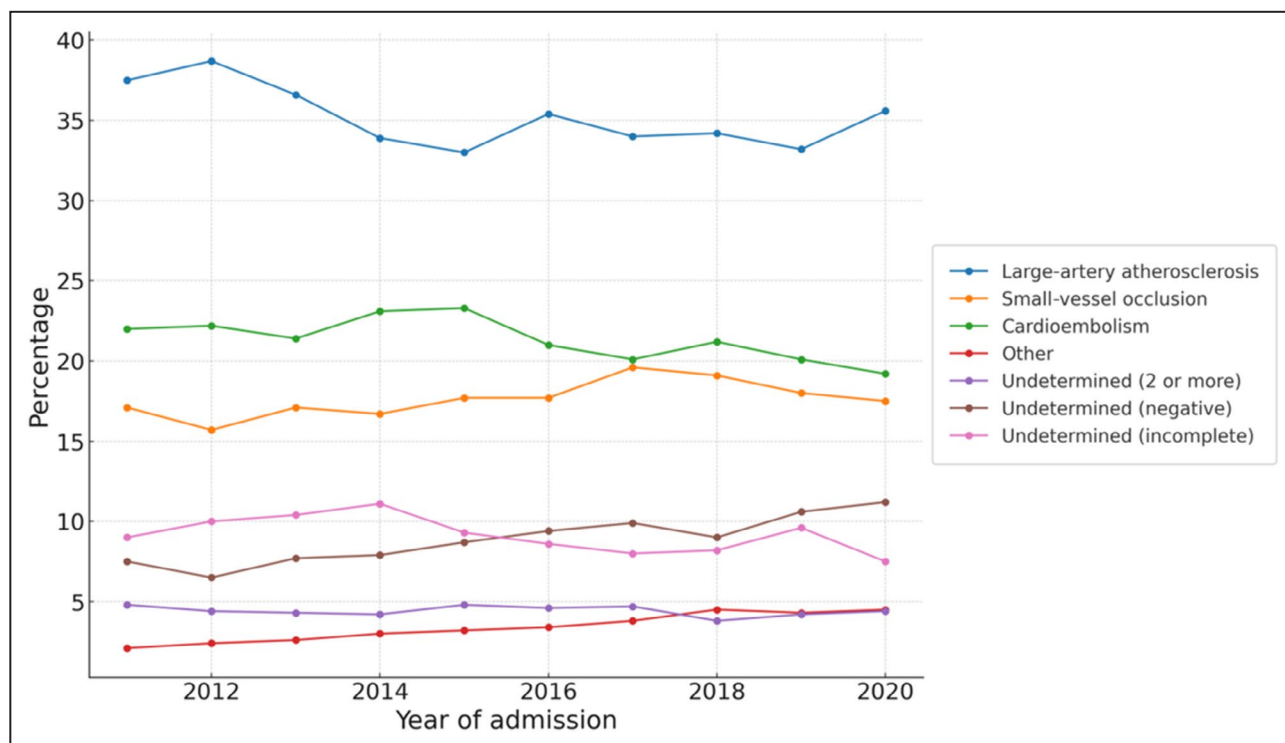


Figure 2. Trends in TOAST subtypes over time (2011–2020).

The proportion of large-artery atherosclerosis decreased slightly ($\beta=-0.018$, $P<0.01$), small-vessel occlusion increased slightly ($\beta=0.01$, $P=0.01$), while cardioembolism decreased ($\beta=-0.029$, $P<0.01$). Adjusted for age and sex (detailed values refer to Table S4). TOAST indicates Trial of ORG 10172 in Acute Stroke Treatment.

Door-to-needle times for IVT remained stable, but the proportion of door-to-puncture times ≤ 60 minutes for EVT increased, albeit slightly ($P<0.01$; Table S5). Increased use of stroke unit care, noninvasive cardiac

evaluations, and prescriptions for dual antiplatelet therapy, NOACs, and statins at discharge was observed (Figures 5 and 6). Dual antiplatelet therapy use notably doubled in patients with noncardioembolic minor stroke

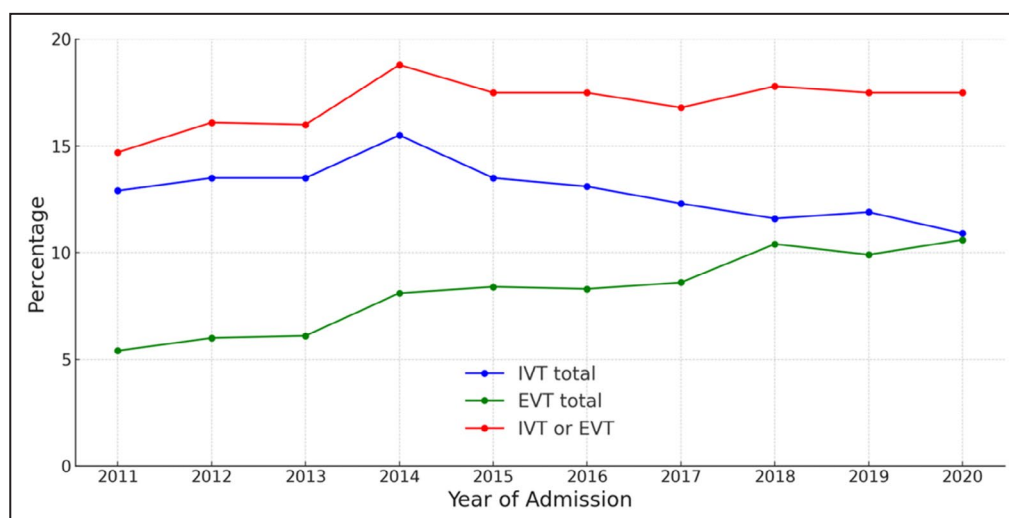


Figure 3. Trends in recanalization therapies over time (2011–2020).

The rate of IVT decreased ($\beta=-0.011$, $P=0.01$), while both the rate of EVT and the combined rate of IVT or EVT increased ($\beta=0.118$, $P<0.01$ and $\beta=0.04$, $P<0.01$, respectively). Adjusted for age, sex, and initial NIHSS score (detailed values refer to Table S5). EVT indicates endovascular thrombectomy; IVT, intravenous thrombolysis; and NIHSS, National Institutes of Health Stroke Scale.

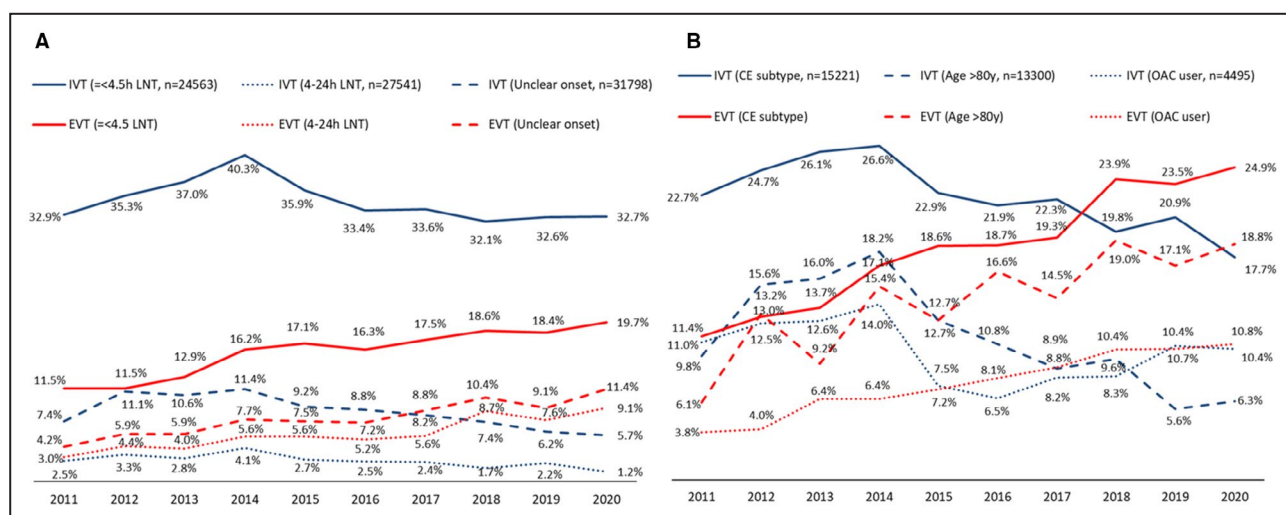


Figure 4. Changes of recanalization therapy rates according to different clinical conditions.

An overall decrease in IVT rates and an increase in EVT rates were observed over the study period among patients with various hospital arrival times after stroke onset (A), as well as in those with cardioembolic subtype, age>80y, and OAC use (B). CE indicates cardioembolism; EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; LNT, last-known-normal time; and OAC, oral anticoagulant.

or high-risk TIA, and statin use in large-artery atherosclerosis and oral anticoagulant use in atrial fibrillation increased, with NOACs surpassing warfarin since 2015.

Outcomes

Neurological deterioration occurred in an average of 10.4% of patients, showing a significant 10-year

decline ($P<0.01$; Figure 7). Conversely, symptomatic hemorrhagic transformation rates following recanalization therapy remained stable at 3.0%. Length of hospital stay has decreased significantly (Table S6).

Three-month outcomes were obtained for 96.2% of the study subjects and 1-year outcomes for 92.1% (Figure S3). There was a marked reduction in mortality rates at both 3 and 12 months (Figure 7 and

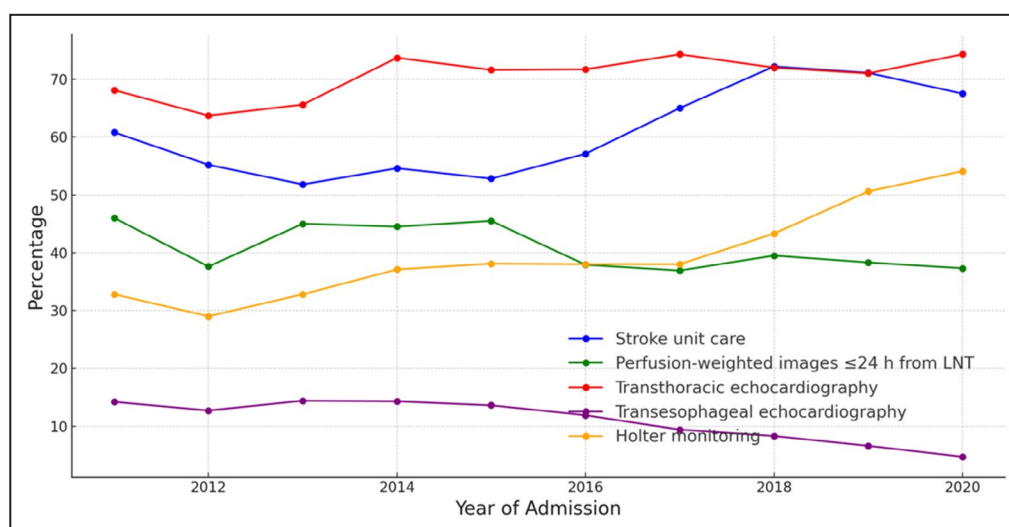


Figure 5. Trends in stroke unit care and diagnostic evaluations over time (2011–2020).

The rates of stroke unit care ($\beta=0.111$, $P<0.01$), transthoracic echocardiography ($\beta=0.035$, $P<0.01$), and Holter monitoring ($\beta=0.115$, $P<0.01$) increased significantly, while the rates of perfusion-weighted images ≤ 24 h from LNT ($\beta=-0.024$, $P<0.01$) and transesophageal echocardiography ($\beta=-0.134$, $P<0.01$) decreased over the period from 2011 to 2020. Adjusted for age, sex, and initial NIHSS Stroke Scale score (detailed values refer to Table S5). LNT indicates last-known-normal time; and NIHSS, National Institutes of Health Stroke Scale.

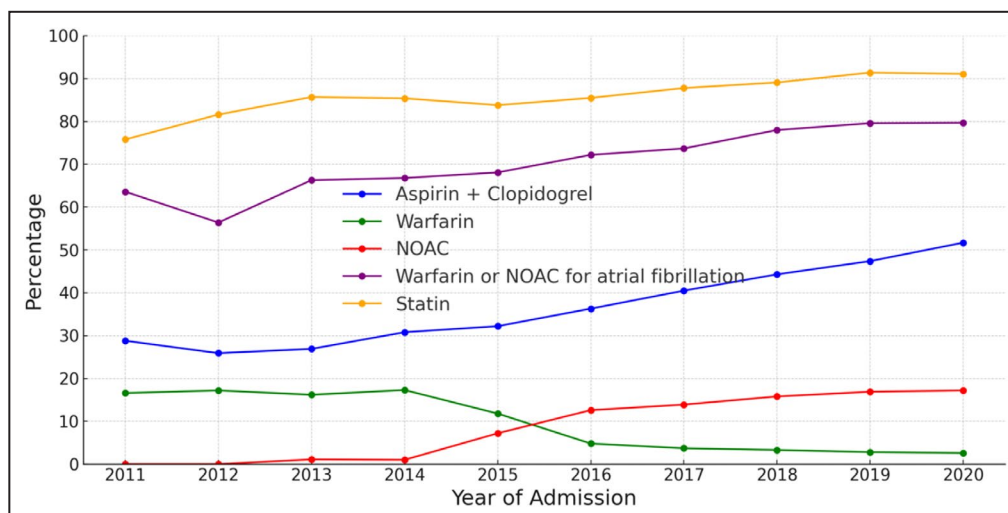


Figure 6. Trends in discharge medications over time (2011–2020).

The rates of using dual antiplatelet agents (aspirin + clopidogrel) ($\beta=0.134$, $P<0.01$), statin use ($\beta=0.112$, $P<0.01$), NOAC ($\beta=0.332$, $P<0.01$), and the combined use of warfarin and NOACs (including apixaban, dabigatran, rivaroxaban, and edoxaban) for atrial fibrillation ($\beta=-0.28$, $P<0.01$) at discharge increased significantly, while the rate of warfarin use ($\beta=-0.28$, $P<0.01$) at discharge decreased significantly over the period from 2011 to 2020. Adjusted for age, sex, and initial NIHSS score (detailed values refer to Table S5). NOAC indicates novel oral anticoagulant; and NIHSS, National Institutes of Health Stroke Scale.

Table S6), peaking in 2014 (8.2% at 3 months and 12.4% at 12 months) before showing a downward trend. Additionally, we observed a significant decrease in the cumulative incidence of recurrent stroke up to 1 year ($P<0.05$). This decline in stroke recurrence

varied across pathogenetic subtypes, with large-artery atherosclerosis and cardioembolism subtypes experiencing notable reductions, whereas the small-vessel occlusion subtype did not (Table S7). The proportions of excellent outcomes with an mRS score of 0 to 1 at

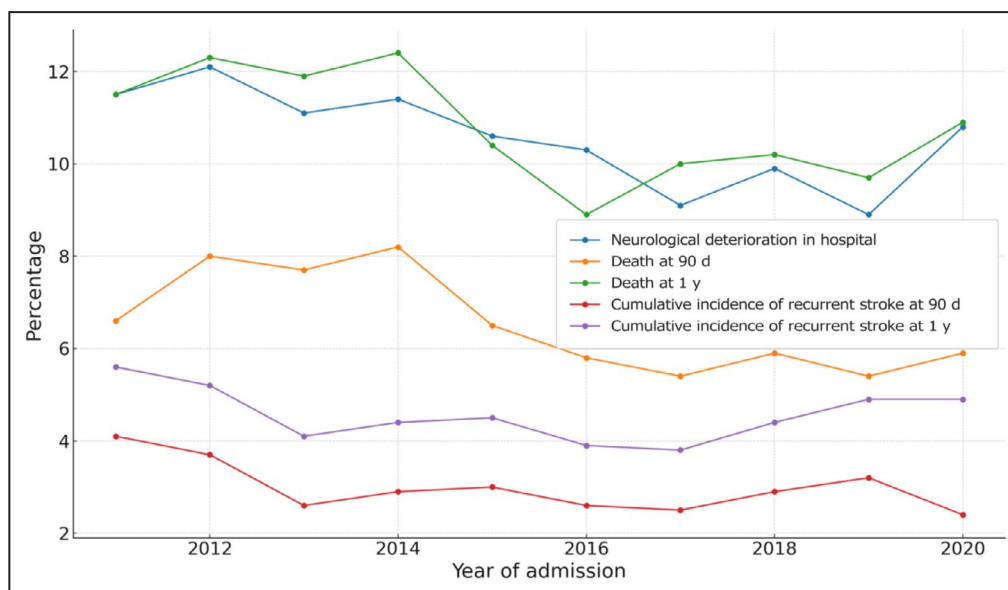


Figure 7. Trends in various stroke outcomes over time (2011–2020).

Neurological deterioration in hospital ($\beta=-0.024$, $P<0.01$), death at 90 days ($\beta=-0.048$, $P<0.01$) and 1 year ($\beta=-0.039$, $P<0.01$), and the cumulative incidence of recurrent stroke at 90 days ($\beta=-0.036$, $P<0.01$) and 1 year ($\beta=-0.043$, $P<0.01$) decreased significantly over the period from 2011 to 2020. Adjusted for age, sex, and initial NIHSS score (detailed values refer to Table S6). NIHSS indicates National Institutes of Health Stroke Scale.

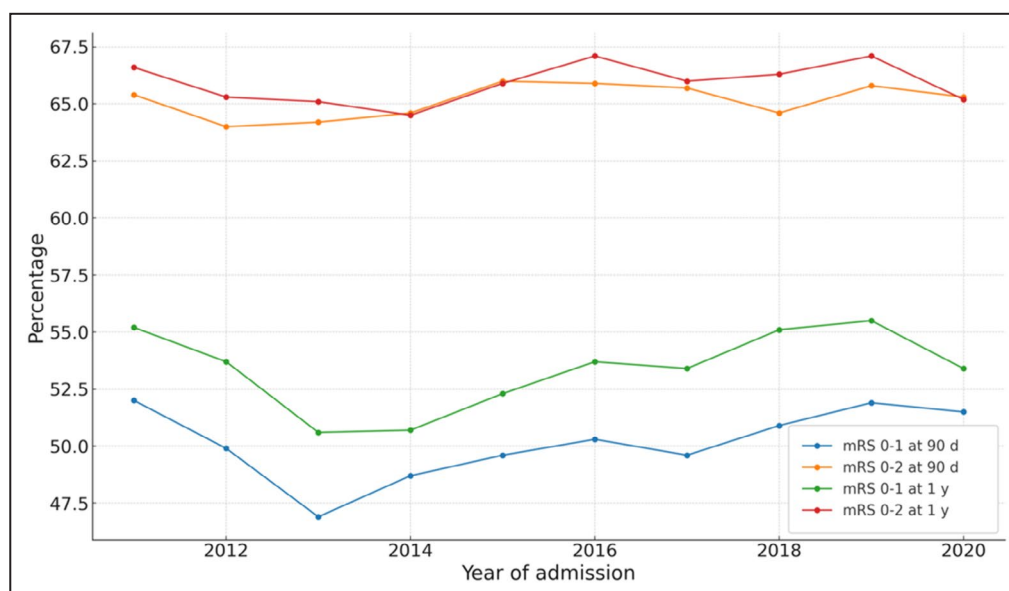


Figure 8. Trends in functional outcomes over time (2011–2020).

Excellent (mRS 0–1) or favorable (mRS 0–2) functional outcomes at 90 days ($\beta=-0.006$, $P=0.06$ and $\beta=-0.005$, $P=0.11$, respectively) and 1 year ($\beta=-0.016$, $P<0.01$; and $\beta=-0.011$, $P<0.01$, respectively) after stroke did not improve over the study period. Adjusted for age, sex, and initial NIHSS Stroke Scale score (detailed values refer to Table S6). mRS indicates modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

3 and 12 months did not show statistically significant differences over the decade (Figure 8 and Table S8).

A post hoc sensitivity analysis tested the robustness of results against potential selection bias from the timing of hospital entry into the study period. Consistent trends were observed in the subgroup of 11 hospitals with continuous involvement throughout the study period across all temporal trends assessed, although trends for these hospitals were no longer significant for mRS scores 0 to 2 at 1 year and cumulative incidence of recurrent stroke at 7 days (Tables S9 through S11).

DISCUSSION

In our analysis of 77 662 patients with acute ischemic stroke or TIA from the 2011 to 2020 time period in a nationwide multicenter stroke registry, we observed improvement in most stroke outcomes across an aging demographic. This period was characterized by the wide adoption of advanced treatments like EVT, NOAC, dual antiplatelet therapy, statin, and stroke unit care. Despite these advancements, we observed a stagnation in functional outcomes, and a decline in the use of IVT over the years.

Our study might be the first to document changes in the occurrence of neurological deterioration during hospitalization, a condition often linked to stroke progression or recurrence and associated with poorer

outcomes.¹² Additionally, the observed decline in stroke recurrence, especially in large-artery atherosclerosis and cardioembolism subtypes, is also a notable finding. The reductions in neurological deterioration and stroke recurrence could be explained at least in part by increased use of stroke unit care,²³ dual antiplatelet therapy,^{5,6} NOACs,^{2–4,24} and statins.^{7,8} However, direct evidence of these treatments preventing neurological deterioration is yet to be established. Enhanced diagnostic approaches, including more frequent use of diffusion-weighted imaging and angiographic and cardiac evaluations, also may have contributed to these improvements through better identification, leading to treatment of specific underlying causes of stroke.

The observed decline in ischemic stroke death in recent decades^{13–15} can be attributed to better control of vascular risk factors²⁵ and advancements in in-hospital management.²⁶ Interestingly, this decline became more pronounced following 2015, aligning with the seminal EVT trials,^{27–29} with our data indicating a peak in mortality rate in 2014 followed by a notable decrease from 2015 onwards (Figure 7). Additionally, the observed reduction in stroke severity may have contributed to improved outcomes. However, our analysis, adjusted for stroke severity, indicates that outcomes have improved independently of stroke severity, suggesting other contributing factors to these positive trends.

Contrary to other studies indicating a rise in major vascular risk factors,^{14,16,30} our study found an

unexpected decrease in the prevalence of hypertension and atrial fibrillation, despite an older population. In Korea, hypertension management has improved considerably, leading to a reduced prevalence of hypertension in the general population from 1998 to 2018.³¹ Additionally, the increased use of oral anticoagulants for atrial fibrillation, particularly since the introduction of NOAC reimbursement in South Korea for high-risk patients in 2015, may explain the declining prevalence in patients with ischemic stroke.⁹ The rise in newly diagnosed atrial fibrillation cases could be attributed to enhanced primary prevention and increased cardiac evaluation. However, the stable proportion of most newly diagnosed risk factors during hospitalization over the decade suggests that primary prevention efforts still leave room for improvement.

The observed reductions in large-artery atherosclerosis and cardioembolic subtypes may also be linked to improved preventive strategies. The decline in large-artery atherosclerosis, mirroring trends seen in Western countries,³² could be attributed to increased statin use. Similarly, the reduction in cardioembolism might be due to the expanded use of NOACs in patients with atrial fibrillation. The decrease in initial stroke severity observed in our study may also result from prestroke statin³³ or NOAC administration.³⁴ The increase in strokes of unknown pathogenesis highlights the potential need for broader application of advanced diagnostic tools, such as implantable loop recorders, to enhance identification of stroke pathogenesis.

Surprisingly, we did not observe any statistically significant differences in functional outcomes during our study period, contrary to expectations based on international results. A recent Japanese study reported improved functional outcomes with increase in use of acute reperfusion therapy in patients with acute ischemic stroke over 2 decades.¹⁹ However, in our study, the IVT rate decreased after 2014, unlike in other countries, where it has steadily risen in recent years.^{19,35,36} Notably, functional outcomes seemed to improve in patients treated with IVT during our study period (Table S12). This suggests that the declining IVT rate might be a contributing factor to the lack of improvement in overall functional outcomes, despite an increase in EVT rates. This finding highlights a potential area for further investigation and improvement in stroke care strategies.

The decline in IVT rates in our study can be attributed to several factors: a higher proportion of patients with mild strokes, increased prestroke use of oral anticoagulants, and more comorbidities related to an aging population. The simultaneous decrease in IVT and increase in EVT, even among patients arriving within 4.5 hours of stroke or TIA onset, suggests that a rise in IVT-ineligible patients may be driving the reduced IVT rate. This is supported by findings from the

Swiss Stroke Registry, which reported a notably low IVT rate in patients with ischemic stroke with atrial fibrillation on NOACs.³⁴ This contrasts with recent research suggesting the safety of IVT in patients who have taken NOACs within 48 hours before stroke onset.³⁷

The lack of improvement in onset to arrival time highlights another potential area in need of improvement. Innovations in prehospital stroke systems of care are necessary, despite shortened door-to-needle times and decreased neurological deterioration after recanalization therapy (Tables S13 and S14). Factors like an aging population and more older individuals living alone may contribute to delays, warranting further research to address these challenges. Additionally, despite pivotal trials extending the recanalization therapy window,^{38,39} the use of perfusion imaging in patients arriving within 24 hours after onset and those with unclear onset (accounting for 41% of our study population) was lower than anticipated. This underuse represents another potential area in need of novel strategies to improve stroke functional outcomes.

Our study's strengths include a large sample size and consistent data collection using standardized protocols since 2008, encompassing a wide range of outcome variables up to 1 year after stroke. This allowed for a comprehensive examination of trends in stroke outcomes and their key determinants, such as stroke severity, pathogenetic subtypes, and acute treatments. The main analysis using random effects would have accounted for interhospital variability.

However, there are study limitations to consider. First, our participants may not fully represent the South Korean stroke population at large, as the CRCS-K-NIH registry primarily includes tertiary or training hospitals engaged in continuous quality improvement activities. Thus, there might be some differences between our study and the national stroke audit. The rapid adoption of advanced stroke treatments and associated outcomes may be more favorable in our study than in the national audit data. Additionally, as our study population was predominantly Korean and all participating hospitals were in South Korea, ethnic and cultural differences might limit the generalizability of our findings to other settings. Second, the observational nature of this study precludes determining causality between treatment changes and outcomes. For example, a detailed analysis to explain the lack of improvement in functional outcomes is beyond the study's scope but warrants additional research to assess the impact of advanced treatments on functional recovery in real-world settings. Third, despite adjusting for age, sex, and stroke severity, residual confounding factors such as comorbidities, socioeconomic status, and medication adherence might have influenced the results. Fourth, the study period includes 2020, the year the COVID-19 pandemic began. Compared

with 2019, emergency room admissions decreased in 2020, while in-hospital neurological deterioration and mortality rates increased, potentially due to the pandemic. However, when a post hoc analysis excluding the 2020 data was performed, there were no significant changes in the trends of most study variables (Tables S15 through S17). The impact of COVID-19 on these trends will be analyzed in a separate study.

In summary, our study reveals that in South Korea over the past decade, most clinical outcomes for patients with acute ischemic stroke or TIA have improved, with the notable exception of functional outcomes. During this period, there also has been a steady increase in the use of treatments proven to be effective in acute stroke treatment and subsequent prevention. However, our results highlight several challenges that need to be addressed to improve quality of stroke care. Additional efforts to develop prehospital stroke systems to reduce onset to arrival time and increase the IVT rate promise to prove useful. Furthermore, research to investigate whether the observed trends, including decreased IVT rates and stagnation of functional outcomes, are unique to South Korea or represent broader trends in countries with older populations and represent an area worthy of risk mitigation related to the root causes of the findings.

ARTICLE INFORMATION

Received May 20, 2024; accepted January 21, 2025.

Affiliations

Department of Neurology, Seoul Medical Center, Seoul, Korea (T.H.P.); Department of Neurology, Ilsan Paik Hospital, Inje University, Goyang, Korea (K.-S.H., Y.-J.C.); Department of Neurology, Dongguk University Ilsan Hospital, Goyang, Korea (W.-S.R., D.-E.K.); Department of Neurology, Chonnam National University Hospital, Gwangju, Korea (M.-S.P., K.-H.C., J.-T.K.); Department of Neurology, Cerebrovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea (J.K., B.-J.K., M.-K.H., H.-J.B.); Department of Neurology, Yeungnam University Hospital, Daegu, Korea (J.L.); Department of Neurology, Dong-A University Hospital, Busan, Korea (J.-K.C., D.-H.K.); Department of Neurology, Eulji University Hospital, Eulji University, Daejeon, Korea (J.G.K., S.-J.L.); Department of Neurology, Ulsan University College of Medicine, Ulsan, Korea (J.-H.K., W.-J.K.); Department of Neurology, Chungbuk National University Hospital, Cheongju, Korea (D.-I.S., K.-S.Y.); Department of Neurology, Keimyung University Dongsan Medical Center, Daegu, Korea (S.I.S., J.-H.H.); Department of Neurology, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Korea (J.C.C.); Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, Korea (B.-C.L., K.-H.Y., M.-S.O.); Department of Neurology, Uijeongbu Eulji Medical Center, Eulji University, Uijeongbu, Korea (J.-M.P.); Department of Neurology, Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul, Korea (K.K.); Department of Neurology, Soonchunhyang University Hospital, Seoul, Korea (K.L.); Department of Neurology, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon-si, Gangwon-do, Korea (S.-H.L.); Department of Neurology, Chung-Ang University Hospital, Seoul, Korea (H.-B.J., K.-Y.P.); Asan Medical Center, Clinical Research Center, Seoul, Korea (J.S.L.); Department of Biostatistics, Korea University College of Medicine, Seoul, Korea (J.L.); and Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL (P.B.G.).

Acknowledgments

Author contributions: Study concept and design: Drs T. H. Park and Bae; acquisition of the data: Drs K.-S. Hong, Cho, Ryu, D.-E. Kim, M.-S. Park, K.-H.

Choi, J.-T. Kim, Kang, B.-J. Kim, Han, J. Lee, Cha J-K D.-H. Kim, J. K. Kim, S. J. Lee, Kwon, W.-J. Kim, Shin, Yum, Sohn, J.-H. Hong, Choi, B.-C. Lee, Yu, Oh, J.-M. Park, Kang, K. Lee, S.-H. Lee, Jeong, and K.-Y. Park; analysis and interpretation of the data: Drs T. H. Park, Bae, J. S. Lee, and J. Lee. The initial draft of the manuscript was prepared by Dr. T. H. Park, and all authors provided critical reviews and approved the final manuscript for submission.

Sources of Funding

This research was supported by a fund (2023-ER1006-00) by Research of Korea Centers for Disease Control and Prevention.

Disclosures

None.

Supplemental Material

Tables S1–S17

Figures S1–S3

REFERENCES

- Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: [10.1016/S0140-6736\(16\)00163-X](https://doi.org/10.1016/S0140-6736(16)00163-X)
- Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. doi: [10.1056/NEJMoa0905561](https://doi.org/10.1056/NEJMoa0905561)
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. doi: [10.1056/NEJMoa1009638](https://doi.org/10.1056/NEJMoa1009638)
- Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: [10.1056/NEJMoa1215340](https://doi.org/10.1056/NEJMoa1215340)
- Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the Point Investigators. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379:215–225.
- Amarencu P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, Silleesen H, Simunovic L, Szarek M, Welch KM, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559.
- Amarencu P, Kim JS, Labreuche J, Charles H, Abtan J, Bejot Y, Cabrejo L, Cha JK, Ducrocq G, Giroud M, et al. A comparison of two LDL cholesterol targets after ischemic stroke. *N Engl J Med*. 2020;382:9–19. doi: [10.1056/NEJMoa1910355](https://doi.org/10.1056/NEJMoa1910355)
- Lee SR, Choi EK, Han KD, Cha MJ, Oh S, Lip GYH. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: a nationwide population-based study. *PLoS One*. 2017;12:e0189495. doi: [10.1371/journal.pone.0189495](https://doi.org/10.1371/journal.pone.0189495)
- Rai AT, Crivera C, Kalsekar I, Kumari R, Patino N, Chekani F, Khanna R. Endovascular stroke therapy trends from 2011 to 2017 show significant improvement in clinical and economic outcomes. *Stroke*. 2019;50:1902–1906.
- Abdul-Rahim AH, Fulton RL, Frank B, Tattisumak T, Paciaroni M, Caso V, Diener HC, Lees KR; VISTA collaborators. Association of improved outcome in acute ischaemic stroke patients with atrial fibrillation who receive early antithrombotic therapy: analysis from VISTA. *Eur J Neurol*. 2015;22:1048–1055.
- Park TH, Lee JK, Park MS, Park SS, Hong KS, Ryu WS, Kim DE, Park MS, Choi KH, Kim JT, et al. Neurologic deterioration in patients with acute ischemic stroke or transient ischemic attack. *Neurology*. 2020;95:e2178–e2191. doi: [10.1212/WNL.0000000000010603](https://doi.org/10.1212/WNL.0000000000010603)

13. Lecoffre C, de Peretti C, Gabet A, Grimaud O, Woimant F, Giroud M, Béjot Y, Olié V. National Trends in patients hospitalized for stroke and stroke mortality in France, 2008 to 2014. *Stroke*. 2017;48:2939–2945. doi: [10.1161/STROKEAHA.117.017640](https://doi.org/10.1161/STROKEAHA.117.017640)
14. Yafasova A, Fosbøl EL, Christiansen MN, Vinding NE, Andersson C, Kruuse C, Johnsen SP, Gislason GH, Torp-Pedersen C, Køber L, et al. Time trends in incidence, comorbidity, and mortality of ischemic stroke in Denmark (1996–2016). *Neurology*. 2020;95:e2343–e2353. doi: [10.1212/WNL.00000000000010647](https://doi.org/10.1212/WNL.00000000000010647)
15. Rücker V, Wiedmann S, O'Flaherty M, Busch MA, Heuschmann PU. Decline in regional trends in mortality of stroke subtypes in Germany from 1998 to 2015. *Stroke*. 2018;49:2577–2583.
16. Hsieh CY, Wu DP, Sung SF. Trends in vascular risk factors, stroke performance measures, and outcomes in patients with first-ever ischemic stroke in Taiwan between 2000 and 2012. *J Neurol Sci*. 2017;378:80–84. doi: [10.1016/j.jns.2017.05.002](https://doi.org/10.1016/j.jns.2017.05.002)
17. Leifheit EC, Wang Y, Goldstein LB, Lichtman JH. Trends in 1-year recurrent ischemic stroke in the US Medicare fee-for-service population. *Stroke*. 2022;53:3338–3347. doi: [10.1161/STROKEAHA.122.039438](https://doi.org/10.1161/STROKEAHA.122.039438)
18. Rücker V, Heuschmann PU, O'Flaherty M, Weingärtner M, Hess M, Sedlak C, Schwab S, Kolominsky-Rabas PL. Twenty-year time trends in long-term case-fatality and recurrence rates after ischemic stroke stratified by etiology. *Stroke*. 2020;51:2778–2785.
19. Toyoda K, Yoshimura S, Nakai M, Koga M, Sasahara Y, Sonoda K, Kamiyama K, Yazawa Y, Kawada S, Sasaki M, et al. Twenty-year change in severity and outcome of ischemic and hemorrhagic strokes. *JAMA Neurol*. 2022;79:61–69. doi: [10.1001/jamaneurol.2021.4346](https://doi.org/10.1001/jamaneurol.2021.4346)
20. Bae HJ; CRCS-K Investigators. David G. Sherman lecture award: 15-year experience of the nationwide multicenter stroke registry in Korea. *Stroke*. 2022;53:2976–2987.
21. Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, Yu KH, Cha JK, Kim DH, Lee J, et al. Current status of acute stroke management in Korea: a report on a multicenter, comprehensive acute stroke registry. *Int J Stroke*. 2014;9:514–518. doi: [10.1111/ijs.12199](https://doi.org/10.1111/ijs.12199)
22. Park H-K, Kim S-E, Cho Y-J, Kim JY, Oh H, Kim BJ, Kang J, Lee K-J, Jang MU, Park J-M, et al. Quality of acute stroke care in Korea (2008–2014): retrospective analysis of the nationwide and nonselective data for quality of acute stroke care. *Eur Stroke J*. 2019;4:337–346. doi: [10.1177/2396987319849983](https://doi.org/10.1177/2396987319849983)
23. Roquer J, Rodriguez-Campello A, Gomis M, Jimenez-Conde J, Cuadrado-Godia E, Vivanco R, Giralt E, Sepulveda M, Pont-Sunyer C, Cucurella G, et al. Acute stroke unit care and early neurological deterioration in ischemic stroke. *J Neurol*. 2008;255:1012–1017. doi: [10.1007/s00415-008-0820-z](https://doi.org/10.1007/s00415-008-0820-z)
24. Seiffge DJ, Traenka C, Polymeris A, Hert L, Peters N, Lyrer P, Engelter ST, Bonati LH, De Marchis GM. Early start of DOAC after ischemic stroke: risk of intracranial hemorrhage and recurrent events. *Neurology*. 2016;87:1856–1862. doi: [10.1212/WNL.0000000000003283](https://doi.org/10.1212/WNL.0000000000003283)
25. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:315–353. doi: [10.1161/01.str.0000437068.30550.cf](https://doi.org/10.1161/01.str.0000437068.30550.cf)
26. Minnerup J, Wersching H, Unrath M, Berger K. Explaining the decrease of in-hospital mortality from ischemic stroke. *PLoS One*. 2015;10:e0131473. doi: [10.1371/journal.pone.0131473](https://doi.org/10.1371/journal.pone.0131473)
27. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20.
28. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018.
29. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: [10.1056/NEJMoa1414905](https://doi.org/10.1056/NEJMoa1414905)
30. Tan BYQ, Tan JTC, Cheah D, Zheng H, Pek PP, De Silva DA, Ahmad A, Chan BPL, Chang HM, Kong KH, et al. Long-term trends in ischemic stroke incidence and risk factors: perspectives from an Asian stroke registry. *J Stroke*. 2020;22:396–399. doi: [10.5853/jos.2020.00878](https://doi.org/10.5853/jos.2020.00878)
31. Kim HC, Lee H, Lee HH, Seo E, Kim E, Han J, Kwon JY; Korean Society of Hypertension (KSH)–Hypertension Epidemiology Research Working Group. Korea hypertension fact sheet 2021: analysis of nationwide population-based data with special focus on hypertension in women. *Clin Hypertens*. 2022;28:1.
32. Ornello R, Degan D, Tiseo C, Di Carmine C, Perciballi L, Pistoia F, Carolei A, Sacco S, et al. Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes: a systematic review and meta-analysis. *Stroke*. 2018;49:814–819.
33. Choi JC, Lee JS, Park TH, Cho YJ, Park JM, Kang K, Lee KB, Lee SJ, Ko Y, Lee J, et al. Effect of pre-stroke statin use on stroke severity and early functional recovery: a retrospective cohort study. *BMC Neurol*. 2015;15:120. doi: [10.1186/s12883-015-0376-3](https://doi.org/10.1186/s12883-015-0376-3)
34. Meinel TR, Branca M, De Marchis GM, Nedeltchev K, Kahles T, Bonati L, Arnold M, Heldner MR, Jung S, Carrera E, et al. Prior anticoagulation in patients with ischemic stroke and atrial fibrillation. *Ann Neurol*. 2021;89:42–53. doi: [10.1002/ana.25917](https://doi.org/10.1002/ana.25917)
35. Marko M, Posekany A, Szabo S, Scharer S, Kiechl S, Knoflach M, Serles W, Ferrari J, Lang W, Sommer P, et al. Trends of r-tPA (recombinant tissue-type plasminogen activator) treatment and treatment-influencing factors in acute ischemic stroke. *Stroke*. 2020;51:1240–1247.
36. Suolang D, Chen BJ, Wang NY, Gottesman RF, Faigle R. Temporal trends in stroke thrombolysis in the US by race and ethnicity, 2009–2018. *JAMA*. 2021;326:1741–1743. doi: [10.1001/jama.2021.12966](https://doi.org/10.1001/jama.2021.12966)
37. Meinel TR, Wilson D, Gensicke H, Scheitz JF, Ringleb P, Goganau I, Kaesmacher J, Bae HJ, Kim DY, Kermer P, et al. Intravenous thrombolysis in patients with ischemic stroke and recent ingestion of direct oral anticoagulants. *JAMA Neurol*. 2023;80:233–243. doi: [10.1001/jamaneurol.2022.4782](https://doi.org/10.1001/jamaneurol.2022.4782)
38. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, et al. Extending thrombolysis to 4.5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet*. 2019;394:139–147. doi: [10.1016/S0140-6736\(19\)31053-0](https://doi.org/10.1016/S0140-6736(19)31053-0)
39. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718. doi: [10.1056/NEJMoa1713973](https://doi.org/10.1056/NEJMoa1713973)