

Secular Trends in Ischemic Stroke Characteristics in a Rapidly Developed Country

Results From the Korean Stroke Registry Study (Secular Trends in Korean Stroke)

Keun-Hwa Jung, MD, PhD; Seung-Hoon Lee, MD, PhD; Beom Joon Kim, MD; Kyung-Ho Yu, MD, PhD; Keun-Sik Hong, MD, PhD; Byung-Chul Lee, MD, PhD; Jae-Kyu Roh, MD, PhD; Korean Stroke Registry Study Group

Background—A dynamic change in industry, lifestyle, and healthcare structure brings a corresponding change in disease patterns. Limited data exist with respect to secular trends in stroke epidemiology in Korea, a rapidly developed country.

Methods and Results—We analyzed individual patient data registered the Korean Stroke Registry, a nationwide hospital-based stroke database, between January 2002 and November 2010. Mortality data were obtained from a national death certificate system. Linear or logistic regression analyses were performed to assess secular trends. A total of 46 098 patients were included in this study. Mean $\pm$ SD age was 66.1 ± 12.3 years, and 57.6% of the patients were men. Over the 9-year period, patient ages steadily increased by 0.24 year annually ($P < 0.001$). Risk factor proportions of hypertension, diabetes, smoking, and prior stroke declined slightly ($P < 0.05$ for all). However, dyslipidemia frequency showed a complex pattern of an initial decline and then an increase. For relative proportions of subtypes, cardioembolism increased, small vessel occlusion decreased, and large artery atherosclerosis remained stable. Still, intracranial stenosis overwhelms extracranial stenosis, but extracranial stenosis is on the rise. Arrival within 3 hours increased from 20% to 29%, and reperfusion therapy increased from 5.3% to 7.0%. Age-adjusted all-cause mortality did not decrease at 30 days but decreased at 1 year over time.

Conclusions—During the first decade of 21st century, stroke characteristics in Korea changed, likely because of increased lifespan, westernized lifestyle, and improved public awareness. Stroke experts need to cope with these distinguishing trends to establish a better strategy for prevention and acute therapy. (*Circ Cardiovasc Qual Outcomes*. 2012;5:327-334.)

Key Words: ischemia ■ stroke ■ trends ■ Korea ■ registries

Stroke is a major health burden worldwide.¹⁻⁵ Expansion of the aged population and alarmingly increasing vascular risk factor prevalence in the child and middle-aged populations undoubtedly forecast an exponential increase of stroke burden in the near future.^{3,4} Rates of cardiovascular risk factors and disease phenotypes vary not only by ethnic group, but also across the socioeconomic state of a nation.⁵ The Korean economy has continued a stable and strong growth during the past 3 or 4 decades, and rapid industrial and societal changes have imposed a great impact on disease patterns.⁶ It is widely supposed, but has not been systematically explored, that multiple domains of risk factors, stroke subtypes, and public awareness of and response to acute stroke have changed in Korea. Experiences from Korea can

be informative in establishing stroke prevention strategies and acute care systems in other rapidly developing countries.

Hospital-based stroke registries have well-recognized limitations in generalizability and ability to estimate incidence and prevalence of populations. However, in contrast to population-based epidemiological studies, they generally ensure more-accurate and comprehensive data with regard to demographics, risk factors, stroke etiology, admission pattern, provided care, and clinical outcomes. Accordingly, stroke registries are well suited to defining the secular trends of these multiple domains. The Korean Stroke Registry (KSR) is a multicenter, prospective, hospital-based stroke registry. Launched in 2002, the KSR has collected nationwide data to gain insight into stroke diagnosis and care.⁷ In the

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From the Department of Neurology, Seoul National University Hospital, Seoul, South Korea (K.-H.J., S.-H.L., B.J.K., J.-K.R.); Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, South Korea (K.-H.Y., B.-C.L.); and Department of Neurology, Ilsan Paik Hospital, Inje University, Goyang, South Korea (K.-S.H.).

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Correspondence to Jae-Kyu Roh, MD, PhD, Department of Neurology, Seoul National University Hospital, 101, Daehangno, Jongno-gu, Seoul 110-744, South Korea, e-mail rohjk@snu.ac.kr or Byung-Chul Lee, MD, PhD, Department of Neurology, Hallym University, College of Medicine, 896, Pyungchon, Anyang City, 431-070, South Korea, e-mail ssbrain@hallym.ac.kr.

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present study, we aimed to evaluate recent national trends in clinical characteristics, delay in seeking medical care, reperfusion therapy, and mortality in patients with acute ischemic stroke in Korea.

WHAT IS KNOWN

- Rapid industrial and societal changes can lead to dynamic changes in risk factors, stroke phenotypes, and treatment.
- Korea has achieved a remarkably high level of economic growth in a short period of time.

WHAT THE STUDY ADDS

- The ages of patients with stroke are steadily increasing over time.
- Cardioembolic stroke continues to increase.
- Extracranial artery stenosis is on the rise.
- Arriving at the hospital within 3 hours and reperfusion therapy are increasing.
- Age-adjusted all-cause mortality at 1 year is decreasing.

Methods

Registry Characteristics

In 2002, the Korean Stroke Society launched a task force comprising stroke specialists in neurology from 26 major university hospitals throughout the country as well as recruited hospitals. To date, the 31 educational general hospitals in Korea have phased in the registry system (online-only Data Supplement Table I). The participating hospitals have registered patients with ischemic stroke or transient ischemic attack (TIA) within 7 days after symptom onset. Stroke was diagnosed through clinical symptoms and relevant findings on CT and MRI scans and magnetic resonance angiography. TIA was defined as a sudden focal neurological deficit that completely resolves within 24 hours. The KSR provides a Web-based database (www.strokedb.or.kr) in which each participating hospital can register patient data in real time. An attending physician initially enters the data into the registry, and all records are regularly monitored within a 1- to 2-week interval by dedicated faculty members with stroke expertise at each hospital for completeness and consistency. The steering committee of KSR has monitored data consistency regularly within a 3-month interval and has encouraged consistent registration. Nonetheless, unexpected circumstances, such as change of individual hospital policies and turnover of dedicated staff at each hospital could cause inconsistent registration during a certain period. The guidelines and procedures of this registry were approved by the Institutional Review Board of the Hallym University Sacred Heart Hospital as a delegate of participating hospitals.

Data Acquisition

We acquired all registered data from 31 centers between January 2002 and November 2010. Exclusion criteria were missing demographic information; incomplete (>10%) documentation for all categories; duplication; protocol violations, such as admission after 7 days from onset; and age <16 years. For each patient, we collected data on demographics, risk factors, Trial of RRG 10172 in Acute Stroke Treatment (TOAST) stroke subtypes, stroke onset, prehospital delays, initial stroke severity as measured by the National Institute of Health Stroke Scale (NIHSS), radiological findings of intracranial and extracranial stenosis relevant for the index stroke, and in-hospital management. We also obtained mortality data for each patient from the Korean National Vital Statistics system.

Definition of Variables

Vascular risk factors included hypertension, diabetes mellitus, dyslipidemia, potential source of cardioembolism (CE), smoking, and history of previous stroke. Hypertension was defined as a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mm Hg, and current use of antihypertensive agents. Diabetes mellitus was diagnosed through relevant clinical or drug history or biochemical evidence of at least 2 measurements of fasting blood glucose readings of >126 mg/dL. Dyslipidemia was defined as current use of lipid-lowering agents or at least 2 abnormal serum lipid measurements (total cholesterol >240 mg/dL or low-density lipoprotein cholesterol >160 mg/dL). The presence of a potential source of CE was defined as having 1 of the following high-risk cardiac conditions: mechanical prosthetic valve, mitral stenosis with atrial fibrillation, atrial fibrillation, left atrial or atrial appendage thrombus, sick sinus syndrome, recent myocardial infarction (<4 weeks), left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, and infective endocarditis.⁸ Smoking was defined as a smoking history of >2 pack-years or current smoker.

The stroke mechanisms were determined by TOAST criteria as follows⁸: large artery atherosclerosis (LAA), small vessel occlusion (SVO), CE, stroke of other etiology, and stroke of undetermined etiology. TIA was not classified for a certain etiology in the TOAST criteria. The KSR provides an algorithm protocol for TOAST classification to enhance standardization. All records on stroke subtypes were monitored by faculty members at each hospital for internal consistency and were refined by a regular discussion by the steering committee for external consistency. In LAA subtype, the location of stenosis relevant to the index stroke was classified into intracranial arterial stenosis of anterior circulation (A-ICAS), extracranial arterial stenosis of anterior circulation (A-ECAS), and posterior circulation stenosis. The A-ICAS was defined as >50% luminal narrowing or occlusion of proximal portions of the middle cerebral artery, anterior cerebral artery, and intracranial portion of the internal carotid artery.⁹ The A-ECAS was defined as >50% luminal narrowing or occlusion of extracranial portions of the internal carotid artery and common carotid artery.¹⁰ The posterior circulation stenosis was defined as >50% luminal narrowing or occlusion of the vertebral artery, basilar artery, and posterior cerebral artery.

Statistical Analysis

Baseline characteristics were summarized by mean±SD or number and percentage for each calendar year of stroke diagnosis. Annual trends in age, time interval after onset, and NIHSS scores were estimated by linear regression analyses. Age trend was analyzed separately for men and women. For the binary categorical variables, log-linear Poisson models were used to estimate rates of increase by calendar year. Calendar year was treated as a continuous variable in the analysis. The mortality change was adjusted for age using 10-year age intervals. Results are presented as relative risks (RRs) with 95% CIs. All *P* values are 2 sided, and a 5% level of statistical significance was used. Statistical analyses were performed with SAS STAT version 9.1 software.

Results

Baseline Characteristics of the Patients

A total of 53 542 patients were registered in the KSR during the study period. After a review of the records, we excluded 7444 patients because of missing demographic information and incomplete (>10%) documentation for all categories (n=2922); duplicate registrations (n=2061) from early referral to another hospital, recurrences, or registration errors; protocol violations (n=2461), such as admission after 7 days of onset; and age <16 years. The numbers of excluded cases according to each hospital and year are shown in online-only Data Supplement Table I. There were no significant changes

in the exclusion number among the years or the hospitals, but clinical characteristics of the excluded cases differed from those of the study population with respect to age, risk factors, NIHSS score, and prehospital delay (online-only Data Supplement Table II).

Finally, 46 098 patients with ischemic stroke and TIA were included in the current study. The mean age was 66.1 ± 12.3 years, and 26 566 (57.6%) were men. Women were older than men (69.2 ± 11.9 versus 63.9 ± 12.1 years, $P < 0.001$). There were 42 981 (93.2%) ischemic strokes and 3117 (6.8%) TIAs. Hypertension was the most common vascular risk factor (29 266 patients [63.5%]) followed by smoking (33.0%), diabetes mellitus (30.1%), prior stroke (19.7%), potential sources of CE (19.4%), and dyslipidemia (19.3%). Detailed data for the baseline characteristics of the study population are shown in online-only Data Supplement Table II.

Secular Trends

Demographic and Risk Factors

Table 1 and Figure 1 show the secular trends by age, sex, and vascular risk factors expressed as the regression coefficient (β) and RR from linear and log-linear Poisson regression analysis, respectively. Ages at stroke onset have increased over time ($\beta = 0.237$ per calendar-year; 95% CI, 0.186–0.288; $P < 0.001$). When stratified by sex, the increasing trend was more prominent in women than in men (Figure 1). The proportion by sex was not significantly changed ($P = 0.193$). For risk factors, frequencies of hypertension, diabetes mellitus, smoking, and prior stroke have decreased statistically ($P < 0.001$), but the changes were not substantial. A complex pattern was noted for dyslipidemia. Its frequency decreased slowly from 2002 to 2007 and then increased again after

2008. Frequency of potential source of CE remained stable during the study period.

Stroke Subtypes

Of 46 098 patients, 36 191 with ischemic stroke were subjected to the stroke subtype analysis after excluding 3117 with TIA (6.8%) and 6790 with missing values based on TOAST classification (14.7%). LAA stroke was the most frequent stroke subtype (36.1%) followed by SVO (25.4%), CE (17.1%), and other (stroke of other etiology, 1.8%; stroke of undetermined etiology, 19.6%). In Poisson regression models, the relative proportion of SVO decreased, with an RR of 0.96 per year (95% CI, 0.95–0.97) between 2002 and 2010, whereas CE increased, with an RR of 1.06 per year (95% CI, 1.05–1.08) during the same period ($P < 0.001$) (Table 2). This trend in the stroke subtype is also shown in Figure 2A. The relative proportion of LAA did not show any directional trend across time periods over the 9 years of the study. Although stroke of undetermined etiology proportions have decreased (RR, 0.99; $P = 0.021$), extensive investigation still failed to define stroke mechanisms in one sixth of the patients. Stroke of other etiology proportions have increased (RR, 1.08; $P < 0.001$), but its contributions were minute at $< 3\%$.

Distribution of Stenoocclusive Lesions

Of 13 061 patients with LAA subtype, angiographic data were available for 11 123 (85.2%). Stenoocclusive lesions relevant for the index stroke were classified into A-ICAS, A-ECAS, A-ICAS+A-ECAS (patients with carotid territory stroke having tandem lesions), and posterior circulation stenosis. Between 2000 and 2010, relative proportions of A-ECAS (RR, 1.07; $P < 0.001$) and posterior circulation stenosis (RR, 1.04; $P < 0.001$) have increased over time,

Table 1. Regression Models of Demographic and Risk Factors, Thrombolysis, and Mortality by Calendar Year of Stroke Diagnosis in Korea, 2002 to 2010

	2002 (n=798)	2003 (n=2738)	2004 (n=4100)	2005 (n=4791)	2006 (n=5501)	2007 (n=5521)	2008 (n=8262)	2009 (n=8294)	2010 (n=6093)	β or RR	95% CI	P Value
Age, y	64.5 ± 11.6	64.8 ± 11.8	65.4 ± 12.1	65.9 ± 12.1	66.0 ± 12.0	66.0 ± 12.4	66.4 ± 12.4	66.6 ± 12.5	66.7 ± 12.6	0.237	0.186–0.288	< 0.001
Male sex	439 (55.0)	1557 (56.9)	2390 (58.3)	2716 (56.7)	3152 (57.3)	3170 (57.4)	4768 (57.7)	4785 (57.7)	3589 (58.9)	1.00	1.00–1.01	0.193
TIA	65 (8.1)	173 (6.3)	265 (6.5)	344 (7.2)	312 (5.7)	347 (6.3)	551 (6.7)	614 (7.4)	446 (7.3)	1.02	1.00–1.03	0.040
HT	527 (66.0)	1805 (65.9)	2729 (66.6)	3046 (63.6)	3486 (63.4)	3356 (60.8)	5201 (63.0)	5340 (64.4)	3776 (62.0)	0.99	0.99–1.00	0.014
DM	250 (31.3)	835 (30.5)	1285 (31.3)	1478 (30.8)	1643 (29.9)	1661 (30.1)	2426 (29.4)	2522 (30.4)	1763 (28.9)	0.99	0.98–1.00	0.042
Dyslipidemia	161 (20.2)	551 (20.1)	938 (22.9)	943 (19.7)	1161 (21.1)	1130 (20.5)	1226 (14.8)	1418 (17.1)	1359 (22.3)	0.98	0.97–0.99	< 0.0001
PSCE	147 (18.4)	494 (18.0)	890 (21.7)	921 (19.2)	1032 (18.8)	999 (18.1)	1590 (19.2)	1746 (21.1)	1146 (18.8)	1.00	0.99–1.01	0.601
Smoking	254 (31.8)	980 (35.8)	1496 (36.5)	1651 (34.5)	1840 (33.4)	1790 (32.4)	2531 (30.6)	2737 (33.0)	1917 (31.5)	0.98	0.98–0.99	< 0.0001
Previous stroke	190 (23.8)	595 (21.7)	921 (22.5)	985 (20.6)	1032 (18.8)	975 (17.7)	1648 (19.9)	1596 (19.2)	1150 (18.9)	0.98	0.97–0.99	< 0.0001
Visit (< 3 h)	161 (20.2)	624 (22.8)	921 (22.5)	1061 (22.1)	1315 (23.9)	1509 (27.3)	2250 (27.2)	2216 (26.7)	1743 (28.6)	1.04	1.03–1.05	< 0.001
Any thrombolysis	42 (5.3)	115 (4.2)	156 (3.8)	252 (5.3)	373 (6.8)	448 (8.1)	630 (7.6)	681 (8.2)	429 (7.0)	1.09	1.07–1.11	< 0.001
rt-PA	35 (4.4)	102 (3.7)	131 (3.2)	194 (4.0)	293 (5.3)	350 (6.3)	533 (6.5)	577 (7.0)	365 (6.0)	1.10	1.08–1.12	< 0.001
30-d mortality	32 (4.0)	110 (4.0)	147 (3.6)	170 (3.6)	195 (3.5)	202 (3.7)	344 (4.2)	335 (4.0)	236 (3.9)	...	...	...
UA	...	...	...	...	...	...	...	...	...	1.01	0.99–1.04	0.211
AA	...	...	...	...	...	...	...	...	...	1.00	0.98–1.02	0.966
1-y mortality	89 (11.2)	369 (13.5)	499 (12.2)	559 (11.7)	639 (11.6)	668 (12.1)	1031 (12.5)	1040 (12.5)	633 (10.4)	...	...	...
UA	...	...	...	...	...	...	...	...	...	0.99	0.98–1.00	0.109
AA	...	...	...	...	...	...	...	...	...	0.97	0.96–0.99	< 0.001

Data are presented as mean $\pm$ SD or n (%), unless otherwise indicated. P value and age were analyzed by linear regression and other categorical variables by log-linear Poisson regression. RR indicates relative risk; TIA, transient ischemic attack; HT, hypertension; DM, diabetes mellitus; PSCE, potential source of cardioembolism; rt-PA, recombinant tissue-type plasminogen activator; UA, unadjusted; AA, age adjusted.

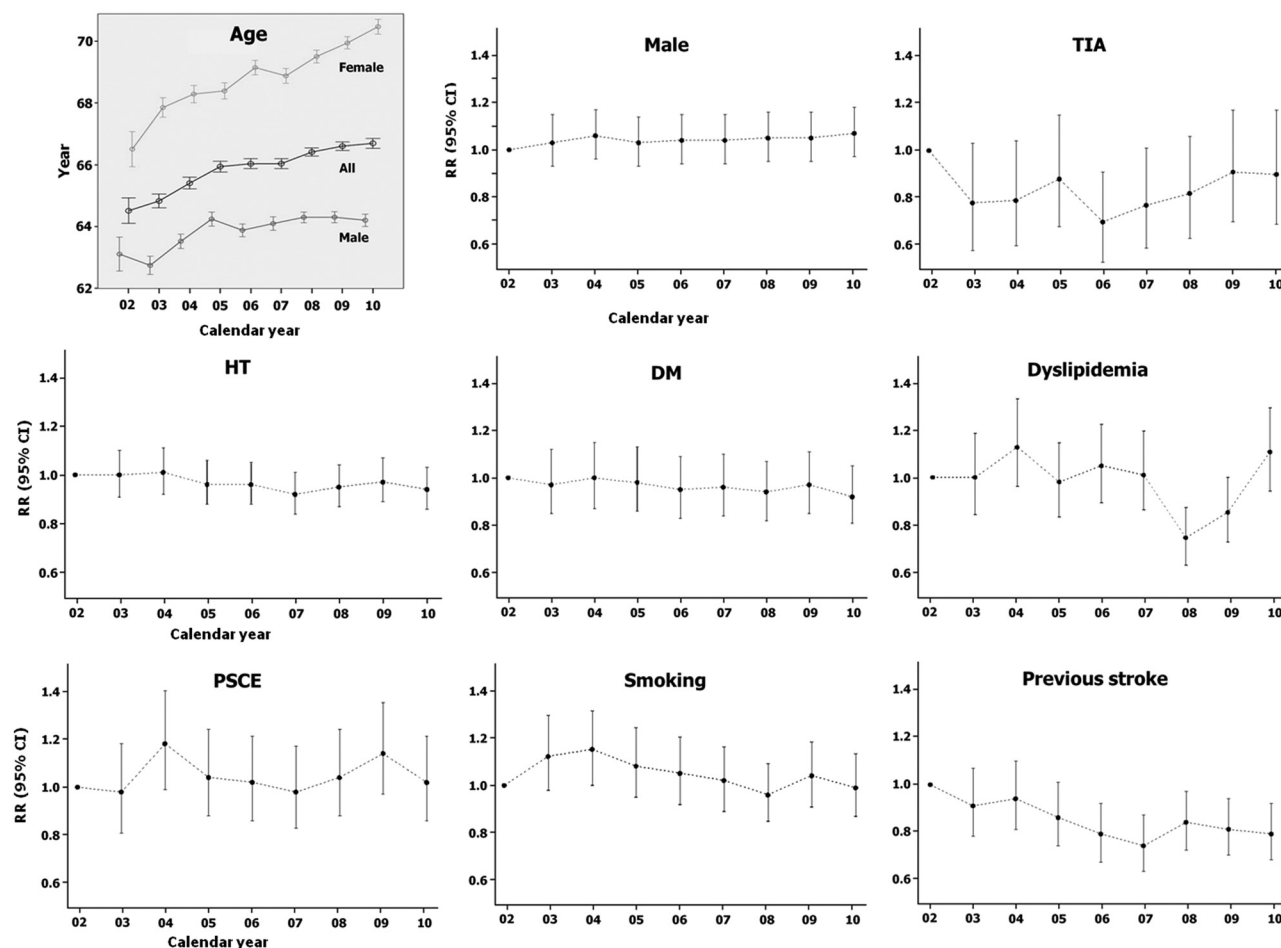


Figure 1. Secular trends for demographic and risk factors among Korean patients with ischemic stroke (2002–2010). The graphs represent age, sex, TIA, and cerebrovascular risk profiles by time period. Estimates were from linear regression (age) or Poisson regression analysis (other variables), with the 2002 group as the reference. DM indicates diabetes mellitus; HT, hypertension; PSCE, potential source of cardioembolism; RR, relative risk; TIA, transient ischemic attack.

whereas the A-ICAS proportion has declined (RR, 0.95; $P<0.001$) (Table 2). This trend in the LAA subtype is also shown in Figure 2B.

Interval of Onset to Arrival and Thrombolysis Rate

For all patients, the average time interval between symptom onset and admission was 28.4 ± 36.0 hours. As shown in online-only Data Supplement Figure I, the time interval has significantly decreased from 31.7 ± 37.6 to 26.8 ± 33.9 hours between 2002 and 2010 ($P<0.001$ for trend). The proportion of patients admitted within 3 hours of symptom onset has increased over time (RR, 1.04; $P<0.001$) (Table 1, Figure 3A) from 20.2% in 2002 to 28.6% in 2010. In concert with the decline in prehospital delay, intravenous recombinant tissue-type plasminogen activator use increased from 4.4% in 2002 to 6.0% in 2010, and any reperfusion therapy increased from 5.3% in 2002 to 7.0% in 2010 (Table 1, Figure 3B).

Stroke Severity on Admission and Mortality

The average NIHSS score was 4 (interquartile range, 2–9), indicating that the majority of enrolled patients had a mild to moderate stroke severity. For patients arriving within 24 hours from onset, the admission NIHSS score markedly declined between 2002 and 2005 ($P<0.001$) (online-only

Data Supplement Figure II), but it did not further decrease after 2005. Overall, all-cause mortality rates were 4% at 30 days and 12% at 1 year (Table 1). Age-adjusted analyses did not show any significant decline in 30-day mortality ($P=0.966$) but demonstrated a significant decline in 1-year mortality ($P<0.001$) (Figure 3C).

Discussion

Changing trends in stroke epidemiology in Korea should be understood in the context of the country's extremely rapid economic growth and globalization. Korea has achieved a remarkably high level of economic growth in a short period of time. Its economy is already the 10th largest in the world, and the rapid pace of its economic development over the past 3 decades is the highest according to the Organization for Economic Cooperation and Development.⁶ In this period of transition, rapid industrial and societal changes could lead to dynamic changes in stroke phenotypes. The current nationwide stroke registry study indicates that even during a 9-year period within the first decade of 21st century, there were notable changes in age, risk factors, stroke subtypes, the public seeking out acute medical care, and reperfusion therapy. Understanding these dynamic trends in patient- and care-related domains could

Table 2. Regression Models of Stroke Subtypes and Distribution of Stenoocclusive Lesions by Calendar Year of Stroke Diagnosis in Korea, 2002 to 2010

	2002 (n=700)	2003 (n=2510)	2004 (n=3774)	2005 (n=4229)	2006 (n=4290)	2007 (n=4277)	2008 (n=6082)	2009 (n=6406)	2010 (n=3923)	RR	95% CI	P Value
LAA	262 (37.4)	950 (37.8)	1299 (34.4)	1494 (35.3)	1462 (34.1)	1572 (36.8)	2204 (36.2)	2363 (36.9)	1455 (37.1)	1.01	1.00–1.01	0.174
SVO	224 (32.0)	706 (28.1)	1124 (29.8)	1174 (27.8)	1142 (26.6)	1052 (24.6)	1436 (23.6)	1433 (22.4)	915 (23.3)	0.96	0.95–0.97	<0.0001
CE	103 (14.7)	331 (13.2)	589 (15.6)	583 (13.8)	634 (14.8)	744 (17.4)	1157 (19.0)	1252 (19.5)	803 (20.5)	1.06	1.05–1.08	<0.0001
SOE	9 (1.3)	22 (0.9)	79 (2.1)	73 (1.7)	62 (1.4)	68 (1.6)	96 (1.6)	140 (2.2)	101 (2.6)	1.08	1.04–1.11	<0.0001
SUE	102 (14.6)	501 (20.0)	683 (18.1)	905 (21.4)	990 (23.1)	841 (19.7)	1189 (19.5)	1218 (19.0)	649 (16.5)	0.99	0.98–1.00	0.021
LAA Subgroup	2002 (n=193)	2003 (n=756)	2004 (n=1125)	2005 (n=1329)	2006 (n=1208)	2007 (n=1345)	2008 (n=1909)	2009 (n=2106)	2010 (n=1152)	RR	95% CI	P Value
A-ICAS	96 (39.7)	404 (53.4)	570 (50.7)	634 (47.7)	565 (46.8)	633 (47.1)	746 (39.1)	824 (39.1)	452 (39.2)	0.95	0.94–0.97	<0.0001
A-ECAS	12 (6.2)	54 (7.1)	113 (10.0)	152 (11.4)	142 (11.8)	184 (13.7)	268 (14.0)	270 (12.8)	153 (13.3)	1.07	1.04–1.09	<0.0001
A-ICAS+A-ECAS	13 (6.7)	55 (7.3)	83 (7.4)	103 (7.8)	111 (9.2)	90 (6.7)	136 (7.1)	170 (8.1)	74 (6.4)	0.99	0.96–1.02	0.650
P-CAS	72 (37.3)	243 (32.1)	359 (31.9)	440 (33.1)	390 (32.3)	438 (32.6)	759 (39.8)	842 (40.0)	473 (41.1)	1.04	1.03–1.06	<0.0001

Data are presented as n (%), unless otherwise indicated. *P* value was analyzed by log-linear Poisson regression. RR indicates relative risk; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; SOE, stroke of other etiology; SUE, stroke of undetermined etiology; A-ICAS, intracranial arterial stenosis of anterior circulation; A-ECAS, extracranial arterial stenosis of anterior circulation; P-CAS, posterior circulation stenosis.

help to guide health providers and policymakers in developing guidelines for stroke prevention and care in Korea as well as in other rapidly developing countries.

The secular changes in demographic and risk factors are likely to impose changes in stroke subtypes, treatment, and outcomes.¹¹ Mean age of patients with stroke increased by >2 years from 64.5 to 66.7 years during the 9-year period,

and the increase was greater in women than in men. Population aging in Korea is projected to be the fastest in the Organization for Economic Cooperation and Development area.⁶ Aging of the present stroke population might be attributable to an increase in life expectancy of the general Korean population, which increased by >4 years from 76.5 years (men, 72.8 years; women, 80.0 years) in 2001 to 80.6

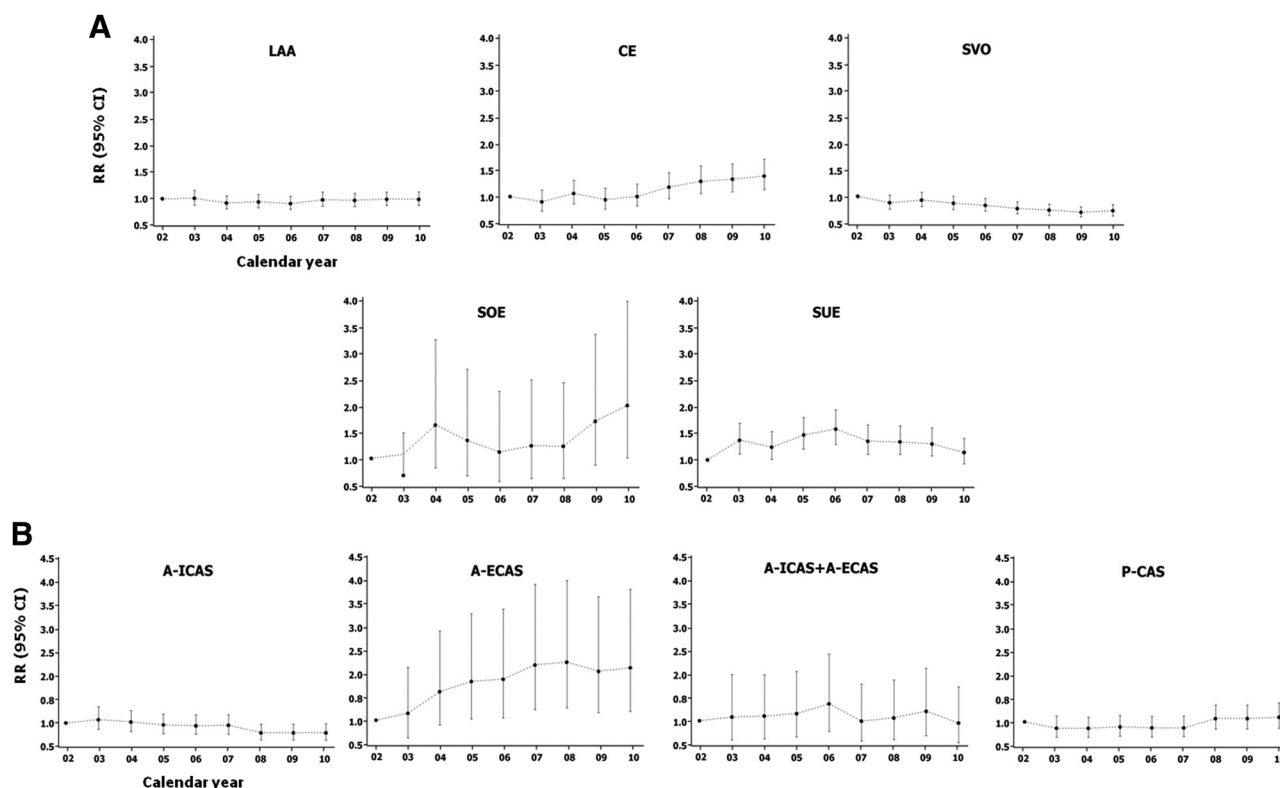


Figure 2. Secular trends for stroke subtypes and distribution of stenocclusive lesions on angiography in the LAA subtype among Korean patients with ischemic stroke (2002–2010). **A**, Subtypes of ischemic stroke by time period. **B**, Distribution of stenocclusive lesions by time period. Data were from 11 123 subjects who had the LAA subtype. Lesion distribution was classified into A-ICAS, A-ECAS, A-ICAS+A-ECAS, and P-CAS. Estimates were from Poisson regression models, with the 2002 group as the reference. A-ICAS indicates extracranial arterial stenosis of anterior circulation; A-ECAS, intracranial arterial stenosis of anterior circulation; CE, cardioembolism; LAA, large artery atherosclerosis; P-CAS, posterior circulation stenosis; RR, relative risk; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; SVO, small vessel occlusion.

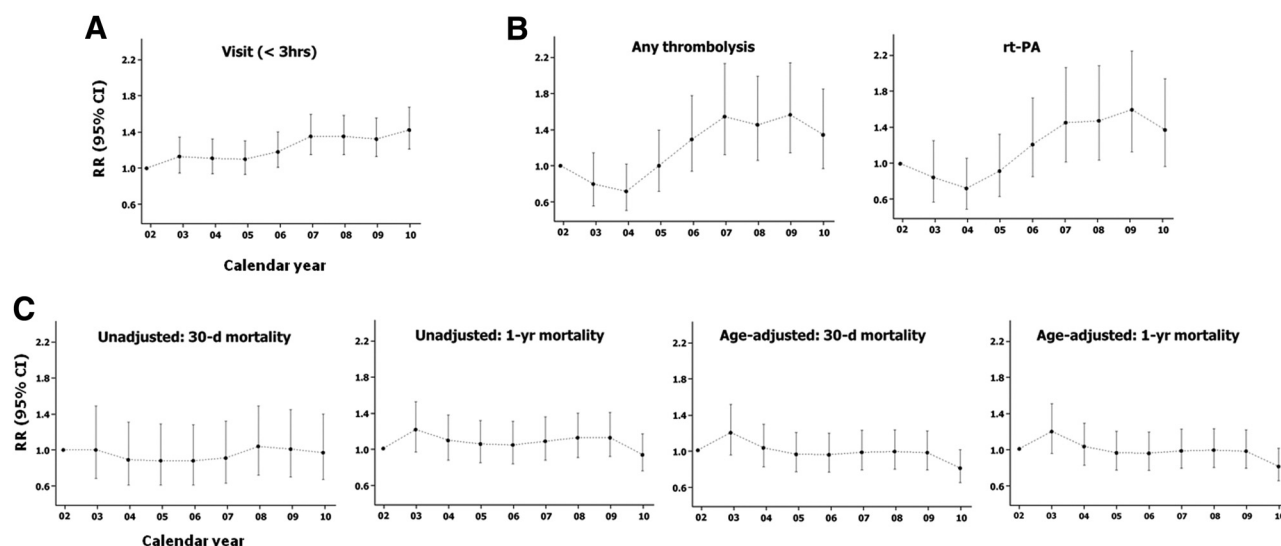


Figure 3. Secular trends for visit within a 3-hour window, thrombolytic therapy, and mortality among Korean patients with ischemic stroke (2002–2010). **A**, Patients who sought evaluation at the hospital within 3 hours after the onset of symptoms by time period. **B**, Patients who underwent any thrombolytic and rt-PA therapy by time period. **C**, Changes in 30-day and 1-year mortality after incident stroke by time period. Estimates were from Poisson regression models, with the 2002 group as the reference. rt-PA indicates recombinant tissue-type plasminogen activator.

years in 2009 (men, 77.0 years; women, 83.8 years).¹² The steep increase of age at stroke onset as well as the general population's life expectancy indicates a continuing increase of elderly patients with stroke who are generally at higher risk for poor prognosis and less responsive to intervention. Accordingly, societal burden of the elderly stroke population would be a significant concern in coming decades in Korea.

Meanwhile, risk factor proportions of hypertension, diabetes, smoking, and prior stroke have declined slightly. A recent systematic review indicates a slowly increasing trend in the prevalence in hypertension, diabetes mellitus, and dyslipidemia in the community.¹³ However, the prevalence in the risk factors can vary depending on survey area, time, and age, sex, and disease distribution of the study population. The ideal stroke registry would be population based. Unfortunately, to date, there has been no systematic investigation for the prevalence of risk factors with respect to Korean ischemic stroke. In practice, it is very difficult to establish such an ideal stroke registry because of methodological and financial limitations. The current study is the first detailed analysis to our knowledge that is based on the KSR, which ensures more-accurate and comprehensive nationwide data.

As widely recognized, hypertension was the most predominant risk factor in the population, but its prevalence in the stroke population decreased over time. In elderly patients, the occurrence of stroke attributable to hypertension is lower than in younger patients.¹⁴ The increase of elderly patients with stroke might be one factor that explains the declining trend of hypertension frequency in the stroke population. On the other hand, hypertension is more closely associated with SVO than with CE.¹⁵ Thus, the relative decrease of SVO and increase of CE would be another factor associated with the declining trend of hypertension frequency. However, taking its high prevalence and proven treatment efficacy in the elderly into account, the finding does not negate the priority of hypertension control for stroke prevention.

Smoking is also a leading risk factor in all stroke subtypes.¹⁶ It should be noted that one third of the patients with stroke were current smokers or had a history of smoking of >2 years, despite its decreasing trend. Compared with the global stroke population enrolled in REACH (Reduction of Atherothrombosis for Continued Health) Registry,¹⁷ the present patients with stroke had a lower rate of current or previous smoking. This low rate is likely attributable to a very low rate of smoking in women. The National Health and Nutrition Survey in 2005 reported that smoking prevalence was 53.3% in men and 5.8% in women aged >15 years in Korea.¹⁸ This gender difference in smoking prevalence in Korea is much higher than in the US population (22.3% in men and 17.4% in women).¹⁹ When restricted to the male stroke population, the rate of current or previous smoking was 52.6% and comparable to or higher than those of other countries. Because smoking is a major preventable risk factor, educational efforts to prevent or stop smoking should be further encouraged.

In the study, dyslipidemia was found in less than one fourth of patients with stroke, which is lower than the 30% to 50% observed in other studies.^{17,20,21} However, it should be noted that we used a high threshold of total cholesterol (>240 mg/dL) and low-density lipoprotein cholesterol (>160 mg/dL) to define dyslipidemia. When we started the KSR registry, definitions of hypercholesterolemia were not unified worldwide, and our threshold was the insurance reimbursement criteria for treating hypercholesterolemia. Therefore, with contemporary criteria applied, the dyslipidemia prevalence would be greater. Hypercholesterolemia within the REACH Registry was present in 67% of the population in Eastern Europe, whereas it is 45% in Asia. For carotid plaque, the prevalence rates ranged from 45.1% in Western Europe to 20.5% in Asia.¹⁷ The present observation of a recent increase in dyslipidemia is consonant with the findings of an earlier study that demonstrated an increasing trend in dyslipidemia prevalence in Asians.²² This changing trend indicates an

adverse transition of vascular risk factors to a more atherogenic profile.

Although the relative proportion of SVO decreased, the proportion of CE increased from 14.7% to 20.5%, which is less than, but still approaching, the 25.6% of CE finding in the German Stroke Data Bank.²³ Increased physician awareness of the importance of CE source detection leading to a more-extensive work-up for this condition would partly explain the increase of CE. Actually, the performance frequency of diagnostic modalities, including transthoracic echocardiography, transesophageal echocardiography, and Holter monitoring, tended to increase across time periods over the 9 years studied (online-only Data Supplement Figure III, online-only Data Supplement Table III), but the changes were not substantial. A prior study reported that even after adjusting for age, atrial fibrillation incidence increased during the past 2 decades.²⁴ If the incidence continuously increases, the projected number of adults with atrial fibrillation would increase by 3-fold from 2000 to 2050.²⁵ Although atrial fibrillation was rare (0.1%–0.5%) in middle-aged patients, the prevalence was 3.5% to 9% in elderly patients.^{6,7} The increasing trend of CE in Korea is likely to be caused by the increased number of elderly patients with atrial fibrillation.^{25,26} The geographical variations of atrial fibrillation within the REACH Registry have been reported to range from 7.7% in Asia to 16% in North America.¹⁷ However, our registry, in which the potential source of CE was classified only into a high-risk or medium-risk source, did not allow us to delineate the change of exact atrial fibrillation prevalence. CE stroke usually is more disabling and fatal and leads to a higher risk for recurrent stroke than other stroke subtypes.¹¹ In Korea, CE stroke is expected to continue increasing and should be aggressively prevented with optimal antithrombotic therapies.

The frequencies of distribution of intracranial and extracranial artery stenosis vary among different races and ethnicities.^{27,28} The ratio of intracranial stenosis to extracranial stenosis was reported be 4:1 in Asian patients with stroke.^{29,30} In Korean patients with stroke, the A-ICAS is still nearly 3 times the A-ECAS, but the ratio markedly decreased from 6.4-fold to 2.9-fold, and the extracranial stenosis is on the rise. Intracranial and extracranial artery stenoses have different risk factors and different pathophysiologies.^{29,30} In an autopsy study of patients with ischemic stroke, unstable plaque was a common cause of extracranial carotid occlusion, but in intracranial occlusion, fibrocalcific narrowing was the main cause of occlusion rather than unstable plaque.²⁹ Westernization of diet, increasing cholesterol level, and obesity in the general population may contribute to the increase of extracranial carotid disease in Korea. Of note, significant relevant A-ICAS+A-ECAS was found in 7% of the LAA subtype. Given that tandem lesions are common in Asian patients with stroke and carry a higher risk for further vascular events or poor outcomes,^{31,32} this patient subgroup would be the subject of future drug or intervention trials.

Prehospital delay is the most important obstacle in thrombolytic therapy. During the study period, hospital arrival within a 3-hour window improved by a relative 43% increase from 20% to 29%, and the thrombolysis rate im-

proved by 1.3-fold from 5.3% to 7.0%. Improved acute care systems and educational programs in the general population and high-risk patients might contribute to these favoring trends. Actually, in 2007, the number of hospital beds; hospital length of stay; and number of physicians, nursing personnel, and consulting physicians in Korea were beyond those of the Organization for Economic Cooperation and Development average and comparable to a high-income country.³³ However, patients arriving within the 3-hour window are still fewer than those of other Asian and western countries.^{34–36} Given that patient or bystander awareness of stroke symptoms have been associated with shorter prehospital delays,^{35,37} expert endeavors to improve public awareness should be continued. Early mortality at 30 days was unchanged over time, whereas long-term mortality at 1 year modestly, but significantly decreased. The absence of detailed information regarding the cause of death did not allow us to fully explore the reason for the discrepant trends between early and long-term mortality rates. The secular improvement of the overall healthcare system could decrease a long-term mortality rate, but the increase in comorbidities and CE stroke according to advancing age could negate the beneficial effects of other factors. Further studies are required to disclose the precise reasons for mortality trends.

This study has several limitations. The findings were derived from a hospital-based registry, and most participating centers were neurology training hospitals. Therefore, the extrapolation of the findings to the general Korean stroke population might be limited. This study did not include all consecutive patients. Of all registered patients, ≈5% were excluded from this analysis because of missing information. In addition, data from patients with stroke who arrived at the emergency department but were not hospitalized were not captured. Nonetheless, this nationwide hospital-based registry has many advantages in that it can clarify diagnoses, classify subtypes, assess risk factors related to etiology, and observe treatment and outcomes.

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Disclosures

None.

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**Secular Trends in Ischemic Stroke Characteristics in a Rapidly Developed Country:
Results From the Korean Stroke Registry Study (Secular Trends in Korean Stroke)**

Keun-Hwa Jung, Seung-Hoon Lee, Beom Joon Kim, Kyung-Ho Yu, Keun-Sik Hong,
Byung-Chul Lee, Jae-Kyu Roh and Korean Stroke Registry Study Group

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SUPPLEMENTAL MATERIAL

Supplementary Table 1. Source population of the participating hospitals

Hospital	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total	Inclusion
										Exclusion, %	
1	175	239	374	419	0	0	388	341	277	2,213	1,912
										301 (13.6)	
2	0	0	233	336	226	329	295	0	0	1,419	1,255
										164 (11.6)	
3	300	445	320	357	349	521	591	881	659	4,423	3,586
										837 (18.9)	
4	61	346	337	339	338	295	318	329	202	2,565	2,207
										358 (14.0)	
5	0	0	0	0	0	0	0	0	100	100	93
										7 (7.0)	
6	61	647	802	0	0	0	655	663	442	3,270	2,893
										377 (11.5)	
7	0	0	0	68	368	328	376	518	364	2,022	1,783
										239 (11.8)	
8	0	0	75	153	120	0	131	118	74	671	586
										85 (12.7)	
9	93	197	222	275	197	0	210	304	207	1,705	1,308
										397 (23.3)	
10	0	0	0	0	272	206	410	460	337	1,685	1,492
										193 (11.5)	
11	114	357	0	534	518	540	505	0	336	2,904 (5.4)	2,481
										423 (14.6)	
12	0	17	441	443	430	233	229	0	191	1,984	1,780
										204 (10.3)	
13	0	0	0	177	220	208	196	188	131	1,120	872
										248 (22.1)	
14	0	0	0	0	133	209	291	240	177	1,050	917
										133 (12.7)	
15	0	0	0	0	107	335	390	332	290	1,454	1,287
										167 (11.5)	
16	0	148	526	555	440	402	455	606	398	3,530	3,018
										512 (14.5)	
17	33	277	263	246	0	574	777	659	0	2,829	2,447
										382 (13.5)	
18	0	6	409	492	614	520	559	482	444	3,526	2,964
										562 (15.9)	
19	0	0	0	136	187	130	257	287	215	1,212	967

										245 (20.2)	
20	0	0	0	16	363	0	734	590	380	2,083	1,964
										119 (5.7)	
21	0	0	135	208	189	194	197	187	159	1,269	1,120
										149 (11.7)	
22	0	0	0	0	39	32	35	31	56	193	174
										19 (9.8)	
23	0	0	0	0	158	273	165	197	99	892	829
										63 (7.1)	
24	0	0	0	0	0	0	117	128	87	332	280
										52 (15.7)	
25	0	0	0	318	551	565	497	501	306	2,738	2,470
										331 (12.1)	
26	0	0	0	0	0	0	57	35	19	111	105
										6 (5.4)	
27	0	0	0	0	0	0	0	177	216	393	340
										53 (13.5)	
28	57	261	281	362	395	424	406	438	336	2,960	2,475
										485 (16.4)	
29	0	0	0	0	0	0	124	349	277	750	689
										61 (8.1)	
30	0	0	0	0	0	0	0	257	212	469	412
										57 (12.2)	
31	71	232	201	161	285	129	203	236	152	1,670	1,455
										215 (12.9)	
Total	965	3,172	4,619	5,595	6,499	6,447	9,568	9,534	7,143	53,542	46,098
Exclusion %	167 (17.3)	434 (13.7)	522 (11.3)	802 (14.3)	995 (15.3)	924 (14.3)	1,305 (13.6)	1,240 (13.0)	1,055 (14.8)	7,442 (13.9)	

Supplementary Table 2. Clinical characteristics of study population and excluded cases in the Korean Stroke Registry.

Parameters	Study population	Excluded cases d/t protocol violation	<i>P</i> value
	46,098	2,461	
Age, yr	66.1±12.3	65.1±14.3	0.001
Male, %	26,566 (57.6)	1,416 (57.5)	0.872
Risk factors			
HT	29,266 (63.5)	1,589 (64.6)	0.263
DM	13,863 (30.1)	839 (34.1)	<0.001
Dyslipidemia	8,887 (19.3)	455 (18.5)	0.330
PSCE	8,965 (19.4)	292 (11.9)	<0.001
Smoking	15,196 (33.0)	741 (30.1)	0.003
Prev. Stroke	9,092 (19.7)	544 (22.1)	0.003
Prehospital delay, hr	28.4±36.0	3062.3±61213.9	<0.001
NIHSS on admission	4 (2-9)	2 (0-5)	<0.001

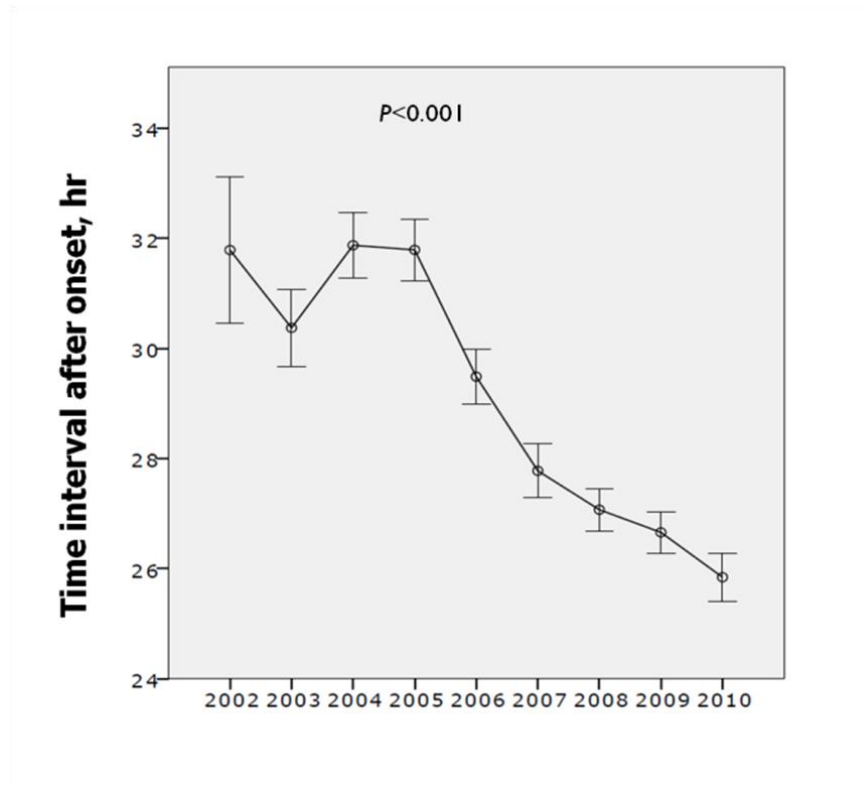
TIA: Transient ischemic attack; HT: hypertension; DM: diabetes mellitus; PSCE: potential source of cardioembolism; NIHSS: National Institute of Health Stroke Scale; *P* value by Student's t-test (continuous values with normal distribution), Mann-Whitney U test (non-normal distribution), or chi-square test (categorical values).

Supplementary Table 3. Regression models of performance of diagnostic work-ups by calendar-year of stroke diagnosis in Korea, 2002-2010.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	RR	Lower	Upper	P-value
	N=798	N=2,738	N=4,100	N=4,791	N=5,501	N=5,521	N=8,262	N=8,294	N=6,093		95% C.I.	95% C.I.	
CT	592	1951	2911	3248	3733	3759	5064	5135	3170	0.96	0.96	0.97	<.0001
	(74.2)	(71.3)	(71.0)	(67.8)	(67.9)	(68.1)	(61.3)	(61.9)	(52.0)				
MRI	737	2510	3815	4421	5048	4864	7659	8023	5489	1.00	1.00	1.01	0.414
	(92.4)	(91.7)	(93.1)	(92.3)	(91.8)	(88.1)	(92.7)	(96.7)	(90.1)				
MRA	726	2473	3614	4091	4885	4666	6107	6601	3995	0.96	0.96	0.97	<.0001
	(91.0)	(90.3)	(88.2)	(85.4)	(88.8)	(84.5)	(73.9)	(79.6)	(65.6)				
TFCA	40	125	251	359	484	571	819	966	521	1.09	1.07	1.10	<.0001
	(5.0)	(4.6)	(6.1)	(7.5)	(8.8)	(10.3)	(9.9)	(11.7)	(8.6)				
TTE	335	1368	2479	3204	4066	3749	5192	5992	3314	1.01	1.01	1.02	<.0001
	(42.0)	(50.0)	(60.5)	(66.9)	(73.9)	(67.9)	(62.8)	(72.2)	(54.4)				
TEE	84	349	474	437	532	493	721	1425	492	1.01	1.00	1.03	0.042
	(10.5)	(12.8)	(11.6)	(9.1)	(9.7)	(8.9)	(8.7)	(17.2)	(8.1)				
Holter	107	537	826	786	980	1211	1588	2326	1047	1.03	1.02	1.04	<.0001
	(13.4)	(19.6)	(20.2)	(16.4)	(17.8)	(21.9)	(19.2)	(28.0)	(17.2)				
TCD	402	1357	2253	2747	3575	2785	4164	4832	2681	0.98	0.98	0.99	<.0001
	(50.4)	(49.6)	(55.0)	(57.3)	(65.0)	(50.4)	(50.4)	(58.3)	(44.0)				

P-value by log-linear Poisson regression analysis, RR: relative risk, C.I.: confidence interval, CT: computed tomography; MRI/A: magnetic resonance imaging/angiography; TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; TCD: transcranial Doppler; TFCA: transfemoral cerebral angiography

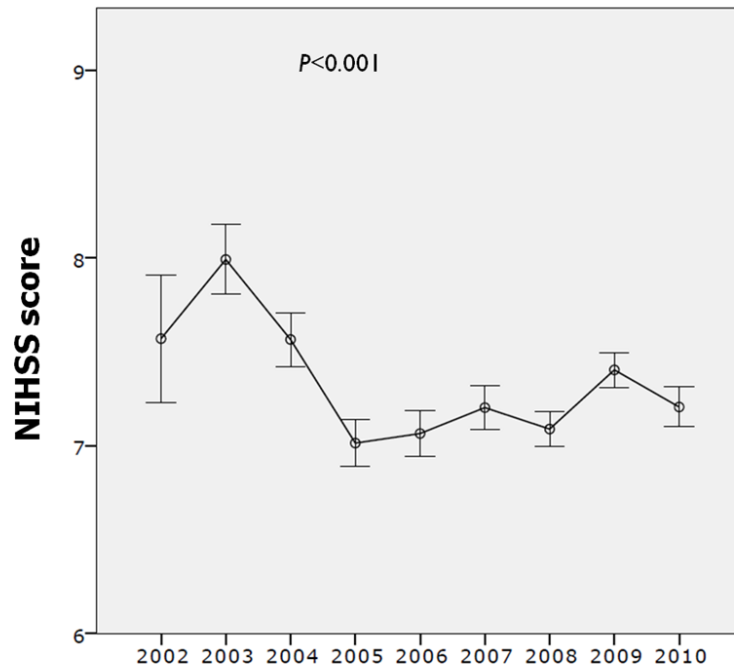
SUPPLEMENTARY FIGURES



Supplementary fig. 1. Secular trends for interval of onset to arrival among Korean ischemic stroke patients (2002-2010).

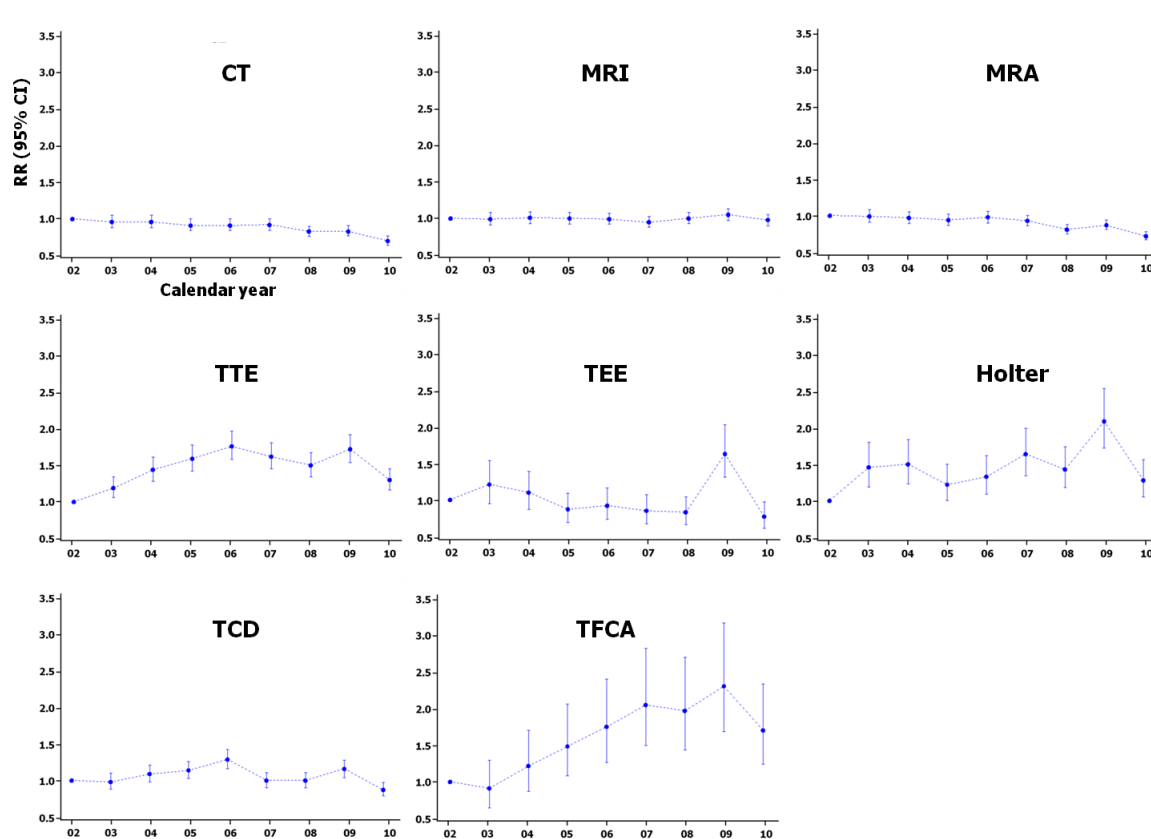
The graph shows the trend in the time interval to visit the hospital after the onset of symptoms.

$P < 0.01$ by linear regression analysis.



Supplementary fig. 2. Secular trends for stroke severity among Korean ischemic stroke patients (2002-2010).

The graph shows the decline in the NIHSS scores in patients with early visit (<24 hr). $P < 0.01$ by linear regression analysis.



Supplementary fig. 3. Secular trends for performance of diagnostic work-ups among Korean ischemic stroke patients (2002-2010).

Graphs represent performance rate of CT, MRI/A, TFCA, TTE, TEE, Holter monitoring, and TCD by time period. Estimates are from Poisson regression models with the 2002-year group as the reference group. Results are presented as relative risks (RRs) with 95% confidence intervals (CIs). CT: computed tomography; MRI/A: magnetic resonance imaging/angiography; TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; TCD: transcranial Doppler; TFCA: transfemoral cerebral angiography

Appendix

Korean Stroke Registry participating centers (in alphabetical order):

Asan Medical Center, Seoul; Bucheon Soonchunhyang University Hospital, Bucheon; Cheju-National University Hospital, Cheju; Cheonan Soonchunhyang University Hospital, Cheonan; Chonnam National University Hospital, Gwangju; Chungbuk National University Hospital, Cheongju; Daejun Eulji University Hospital, Daejun; Dong-A University Medical Center, Busan; Dongguk University Gyeongju Hospital, Gyeongju; Dongguk University Ilsan Hospital, Ilsan; Ewha Woman's University Mokdong Hospital, Seoul; Gachon Gil Medical Hospital, Incheon; Gunsan Medical Center of Wonkwang University Hospital, Gunsan; Gyeongsang National University Hospital, Jinju; Hallym University Sacred Heart Hospital, Anyang; Inha University Hospital, Incheon; Inje University Ilsan Paik Hospital, Ilsan; Inje University Pusan Paik Hospital, Busan; Kangdong Kyunghee Medical Center, Seoul; Kangdong Sacred Heart Hospital, Seoul; Keimyung University Dongsan Hospital, Daegu; Konkuk University Medical Center, Seoul; Kyunghee Medical Center, Seoul; National Health Insurance Corporation Ilsan Hospital, Ilsan; Seoul Metropolitan Boramae Medical Center, Seoul; Seoul Eulji Hospital, Seoul; Seoul Medical Center, Seoul; Seoul National University Bundang Hospital, Bundang; Seoul National University Hospital, Seoul; Seoul Soonchunhyang University Hospital, Seoul; Yeungnam University Medical Center, Daegu