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Risk of Subsequent Events in Patients With Minor Ischemic Stroke or High-Risk Transient Ischemic Attack

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ABSTRACT

This study aimed to present the prognosis after minor acute ischemic stroke (AIS) or transient ischemic attack (TIA), using a definition of subsequent stroke in accordance with recent clinical trials. In total, 9,506 patients with minor AIS (National Institutes of Health Stroke Scale ≤ 5) or high-risk TIA (acute lesions or ≥ 50% cerebral artery steno-occlusion) admitted between November 2010 and October 2013 were included. The primary outcome was the composite of stroke (progression of initial event or a subsequent event) and all-cause mortality. The cumulative incidence of stroke or death was 11.2% at 1 month, 13.3% at 3 months and 16.7% at 1 year. Incidence rate of stroke or death in the first month was 12.5 per 100 person-months: highest in patients with large artery atherosclerosis (17.0). The risk of subsequent events shortly after a minor AIS or high-risk TIA was substantial, particularly in patients with large artery atherosclerosis.

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Keywords: Minor Ischemic Stroke; Ischemic Attack, Transient; Event Outcome; Stroke Recurrence

The positive findings of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE), Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) and The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Aspirin for Prevention of Stroke and Death (THALES) trials has led to the implementation of dual antiplatelet therapy as standard of care during the early period following minor acute ischemic stroke (AIS) or high-risk transient ischemic attack (TIA).[1-4] In all three trials, the stroke endpoint did not distinguish between the progression of initial symptoms during hospitalization due to the index event and subsequent stroke.[2-4] Worsening of existing stroke symptoms would thus be defined as a subsequent stroke using these trial definitions. Until now, there have been no real-world studies that have used this definition of subsequent stroke in accordance with recent clinical trials, and that have used the THALES trial enrollment AIS criterion of National Institutes of Health Stroke Scale (NIHSS) score of ≤ 5. In this study, we assessed the cumulative incidence and incidence rate of outcome events, including the progression of initial stroke symptoms after minor AIS and high-risk TIA, using data from the Clinical Research Collaboration of Stroke in Korea (CRCS-K).[5,6] This study was a secondary analysis using the data set of our prior study about the 1-year outcomes following minor stroke or high-risk TIA.[7]

Patients 20 years or older with minor AIS or high-risk TIA who were admitted to hospital within 7 days of stroke onset to one of 12 participating centers of the CRCS-K between November 2010 and October 2013 were included. Minor AIS was defined as an NIHSS score of ≤ 5, and high-risk TIA was defined by symptom resolution within 24 hours of symptom onset and either: 1) documented acute lesions on diffusion-weighted magnetic resonance imaging (MRI) correlating with relevant symptoms; or 2) ≥ 50% stenosis or occlusion in intracranial or extracranial cerebral arteries, relevant to the symptoms. Information on demographics, stroke risk factors, medication use prior to admission and acute management was collected during index hospitalization. Stroke etiology was defined according to the MRI-based algorithm for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.[8,9]

The primary outcome of this study was a composite of stroke (ischemic or hemorrhagic) and all-cause mortality. Secondary outcomes were stroke and all-cause mortality considered separately. All the events were prospectively captured during index hospitalization, and via a review of electronic medical records or a structured telephone interview up to 1 year after stroke onset.[5,6] Our study used the same definition of ischemic stroke during hospitalization as the CHANCE, POINT and THALES trials, which included either the sudden onset of new focal neurological deficits or the rapid worsening of an existing focal neurological deficit that persisted for > 24 hours and that was not attributable to a non-ischemic cause.[2-4] The worsening of an existing deficit was defined as an increase in the NIHSS score of ≥ 2 in total, or as an increase in the NIHSS subscore 1a, 1b, 1c (level of consciousness), 5a, 5b, 6a or 6b (motor) of ≥ 1.[6,10,11]

Cumulative incidence for the outcomes was calculated at 1 month, 3 months and 1 year after symptom onset using the Kaplan–Meier (product-limit) method. Incidence rate was estimated by dividing the total number of patients with a first event by the total patient time

Disclosure

Authors Lesén E, Hedberg J, Tank A and Fita EG are employees of AstraZeneca. Independent of the submitted work, Bae HJ reports: grants from AstraZeneca Korea, Bayer, BMS Korea, Boehringer Ingelheim, Daichi Sankyo, Dong-A Pharmaceutical, Korean Drug Co. Ltd., Servier, Shin Poong Pharm. Co. Ltd and Yuhan Corporation; grants and personal fees from ESAI-Korea and Shire Korea Ltd; and personal fees from Amgen Asia Holding Limited, and Otsuka Korea outside the submitted work. The other authors report no conflicts.

Author Contributions

Conceptualization: Lee KJ, Park HK, Lesén E, Lee J, Bae HJ. Data curation: Shin DW, Song JE, Lee JS. Formal analysis: Song JE, Lee J. Funding acquisition: Bae HJ. Investigation: Lee KJ, Shin DW, Park HK, Kim BJ, Park JM, Kang K, Park TH, Lee KB, Hong KS, Cho YJ, Kim DE, Ryu WS, Lee BC, Yu KH, Oh MS, Lee SJ, Kim JG, Lee J, Cha JK, Kim DH, Kim JT, Choi KH, Choi JC, Lesén E, Hedberg J, Tank A, Fita EG, Lee JS, Lee J, Bae HJ. Methodology: Lee KJ, Shin DW, Park HK, Kim BJ, Park JM, Kang K, Park TH, Lee KB, Hong KS, Cho YJ, Kim DE, Ryu WS, Lee BC, Yu KH, Oh MS, Lee SJ, Kim JG, Lee J, Cha JK, Kim DH, Kim JT, Choi KH, Choi JC, Lesén E, Lee JS, Lee J, Bae HJ. Project administration: Shin DW. Resources: Kim BJ, Park JM, Kang K, Park TH, Lee KB, Hong KS, Cho YJ, Kim DE, Ryu WS, Lee BC, Yu KH, Oh MS, Lee SJ, Kim JG, Lee J, Cha JK, Kim DH, Kim JT, Choi KH, Choi JC, Bae HJ. Software: Song JE. Supervision: Bae HJ. Validation: Kim BJ, Lesén E, Hedberg J, Tank A, Fita EG. Visualization: Song JE. Writing - original draft: Lee KJ. Writing - review & editing: Bae HJ.

in months in the following predetermined time periods: 0–30 days, 31–90 days and 91 days to 1 year. Comparisons of the crude cumulative incidence and incidence rate in each time period between stroke etiologies were made using the log-rank test and univariate Poisson regression analysis, respectively. Hazard ratios and rate ratios (RRs) of stroke subtypes were estimated using the Cox proportional hazard model and the Poisson regression model, respectively, along with adjustments for predetermined covariates (see **Table 1** footnotes). Patients with other-determined etiologies were excluded from comparisons with stroke etiologies because there were few patients in this category. As an ad hoc analysis, cumulative incidences with additional adjustments (for intravenous thrombolysis, endovascular thrombectomy, number of antiplatelet agents at discharge, and stroke subtype) were calculated. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA) and R software version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). A *P* value of < 0.05 was considered statistically significant.

A total of 9,506 patients were included in the current analysis (**Supplementary Fig. 1**). The mean age was 65.9 years and 61.2% of patients were male (**Supplementary Tables 1** and **2**). The median (interquartile range) follow-up duration was 369 (361–391) days. For the primary outcome, the 1-month, 3-month and 1-year cumulative incidence was 11.2%, 13.3% and 16.7%, respectively. The incidence of stroke was 10.8%, 12.2% and 14.3%, respectively, and the incidence of all-cause mortality was 0.7%, 1.8% and 4.0%, respectively (**Fig. 1**, **Supplementary Table 3**). The cumulative incidences of these events were similar after adjusting for covariates (**Supplementary Table 4**). The incidence rate was highest during the first 30 days, with 12.5 events per 100 person-months for the primary outcome, followed by 0.8 events per 100 person-months between 31 days and 90 days, and 0.34 events per 100 person-months between 91 days and 1 year. This trend was also observed for stroke and mortality individually (**Supplementary Table 3**).

Patients with large artery atherosclerosis had the highest 1-year cumulative incidence of the primary outcome (20.3%), while patients with small vessel occlusion had the lowest (10.1%). The multivariable Cox regression analysis showed that, compared with small vessel occlusion, large artery atherosclerosis had the highest risk (**Table 1**, **Supplementary Fig. 2**). Between stroke onset and 30 days, the incidence rate was highest in large artery atherosclerosis (17.0 events per 100 person-months; RR, 2.0; 95% confidence interval, 1.6–2.3). However, after the first 30 days, a higher incidence for patients with large artery atherosclerosis compared with other etiologies was no longer observed. Among the secondary outcomes, the observed trends for stroke were similar to those for the primary outcome (**Supplementary Table 5**), although mortality had a less pronounced trend (**Supplementary Table 6**).

Table 1. Cumulative incidence and incidence rate over time for composite of stroke or death, categorized by stroke etiology

Stroke etiology	0–30 days		31–90 days		91 days to 1 year		1-year cumulative incidence	
	Incidence rate (CI)[a]	RR (95% CI)[b]	Incidence rate (CI)[a]	RR (95% CI)[b]	Incidence rate (CI)[a]	RR (95% CI)[b]	Cumulative incidence (CI)	HR (95% CI)[b]
Large artery atherosclerosis (n = 3,659)	17.0 (15.6–18.5)	2.0 (1.6–2.3)	0.8 (0.6–1.0)	2.0 (1.2–3.2)	0.4 (0.3–0.4)	2.6 (1.7–3.9)	20.3 (19.1–21.7)	2.0 (1.8–2.3)
Small vessel occlusion (n = 2,206)	8.5 (7.3–9.8)	Ref	0.4 (0.2–0.5)	Ref	0.1 (0.1–0.2)	Ref	10.1 (8.9–11.4)	Ref
Cardioembolism (n = 1,306)	11.1 (9.4–13.2)	1.3 (1.0–1.6)	1.0 (0.7–1.4)	2.4 (1.4–4.1)	0.4 (0.3–0.6)	3.0 (1.9–4.7)	17.2 (15.2–19.4)	1.6 (1.3–1.9)
Undetermined (n = 2,119)	9.8 (8.5–11.3)	1.2 (0.95–1.4)	1.1 (0.9–1.5)	2.9 (1.8–4.8)	0.4 (0.4–0.5)	3.2 (2.1–4.9)	16.5 (15.0–18.2)	1.6 (1.3–1.9)

P = 0.001, calculated by log-rank test (for RR) or univariate Poisson regression analysis (for HR).
CI = confidence interval, HR = hazard ratio, Ref = reference, RR = rate ratio.
[a]Per 100 person-months.
[b]Adjusted for age, sex, smoking, history of coronary heart disease, history of transient ischemic attack, history of stroke, history of hypertension, history of diabetes mellitus, history of dyslipidemia and year of index date.

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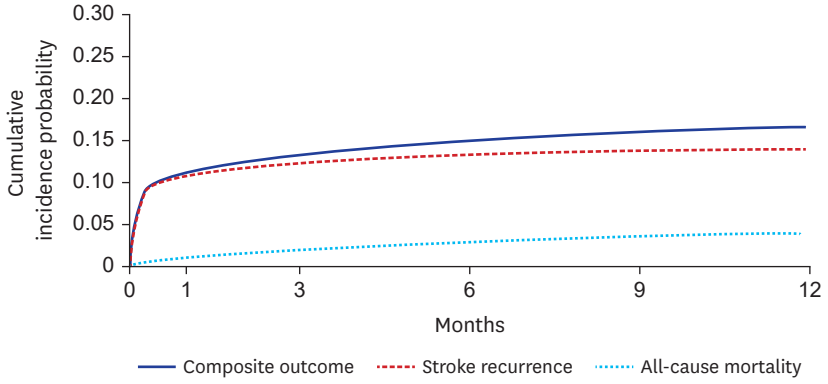

No. at risk						
Composite outcome	9,506	8,387	8,120	7,703	7,594	5,774
Stroke recurrence	9,506	8,387	8,120	7,703	7,594	5,774
All-cause mortality	9,506	9,355	9,178	8,767	8,693	6,678

Fig. 1. Adjusted[a] cumulative incidence of stroke or death (as composite and assessed individually) after minor AIS and TIA.
AIS = acute ischemic stroke, TIA = transient ischemic attack.
[a]Direct adjusted cumulative incidence by Cox proportional hazard regression analysis. Variables adjusted are age, gender, smoking, history of coronary heart disease, history of transient ischemic attack, history of stroke, history of hypertension, history of diabetes mellitus, history of dyslipidemia, history of atrial fibrillation and year of index date.

The CHANCE and POINT trials showed a 90-day risk of stroke of 10.0% and 5.6%, respectively, compared with 12.2% in the current study.[2,3] Furthermore, the 1-year stroke risk in CHANCE was 12.3%,[12] which is slightly lower than that reported by the current study (14.3%). These risks are much higher than the 6.1% reported in our previous study[6] and the 5.1% reported by the TIAregistry.org study,[13] both of which involved patients with minor AIS or high-risk TIA. A potential explanation for this discordance is the possibility that the worsening of existing stroke symptoms was not classified as a subsequent stroke in our previous study or the TIAregistry.org study,[6,13] but may have been defined as a subsequent stroke event in both the CHANCE trial and the current study.

Our findings for stroke etiologies were in line with those of previous studies. A post hoc analysis of CHANCE trial data showed that patients who had a multiple lesion pattern showing on brain MRI scans (who were predominantly patients with large artery atherosclerosis) had a higher risk of stroke than those with no multiple lesion pattern.[14] Our results showed that the incidence rate was high during the early period after cardioembolic stroke, which was concordant with the results of the TIAregistry.org study.[13] This suggests that patients with cardioembolic stroke may be a potential target for intensive treatment during the early period after stroke, which is being examined by the TIMING trial.[15]

There are several limitations to this study. First, because we started outcome event capture after the patient's admission to the hospital (within 7 days of symptom onset), early outcome events occurring before hospitalization were not captured, leading to potential under-reporting of events; and this differs from the enrollment criteria applied in POINT (< 12 hours of symptom onset), CHANCE and THALES (< 24 hours). Second, the participating centers of the CRCS-K registry are mainly tertiary hospitals, which may limit the generalizability of the study results; however, the age and sex distribution of the CRCS-K registry population was shown to be comparable to that of Korean national data on patients with stroke.[16] Third, the loss to follow-up was 5.3% at 1 year in this study; however, such a loss to follow-

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up is not unusual for observational research and a comparable rate has been reported in other real-world studies.[13] Fourth, the results are limited to South Koreans and may not be generalizable to other populations. Fifth, the effect of antithrombotics or risk factor control status was not considered in this analysis.

In conclusion, using an outcome definition in accordance with recent clinical trials, there is a substantial risk of subsequent events shortly after a minor AIS or high-risk TIA. The early risk is particularly high in patients with large artery atherosclerosis, which indicates the necessity of early secondary prevention.

Ethics statement

Collection of data and the waiver of consent because of anonymity and minimal risk to participants was approved by the local Institutional Review Boards (IRBs) of all participating centers. Use of the registry database and analysis for the current study were approved further by the IRB of Seoul National University Bundang Hospital (No. B-1908/561-104).

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Patient baseline characteristics

Click here to view

Supplementary Table 2
Baseline characteristics according to stroke etiology

Click here to view

Supplementary Table 3
Cumulative incidence and incidence rate over time for the composite of stroke or death

Click here to view

Supplementary Table 4
Adjusted[a] cumulative incidence of stroke or death (as a composite and assessed individually) after minor acute ischemic stroke and transient ischemic attack

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Supplementary Table 5
Cumulative incidence and incidence rates of stroke over time, categorized by stroke etiology

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Supplementary Table 6

Cumulative incidence and incidence rates of all-cause mortality over time, categorized by stroke etiology

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Supplementary Fig. 1

Flowchart for selection of study population and categorization into subgroups.

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Supplementary Fig. 2

Adjusted[a] cumulative incidence after minor acute ischemic stroke and transient ischemic attack according to stroke etiology. The three charts show: (**A**) composite of stroke and death, (**B**) stroke, and (**C**) death.

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