Stroke

ORIGINAL CONTRIBUTION

Management Strategies for Early Neurological Deterioration in Noncardioembolic Ischemic Stroke

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BACKGROUND: Early neurological deterioration (END) is a frequent complication of acute ischemic stroke. Although END worsens clinical outcomes, standardized treatment strategies remain undefined, resulting in variability in clinical practice. This study examines real-world treatment patterns for END and compares the effects of different strategies on neurological and functional outcomes.

METHODS: This study analyzed data from a nationwide, prospective, multicenter stroke registry in South Korea, including patients with noncardioembolic stroke who developed END due to stroke progression between January 2019 and August 2024. END was defined as new or worsening neurological symptoms meeting National Institutes of Health Stroke Scale criteria (≥2-point total or ≥1 point in consciousness or motor subscores) with radiological confirmation. Patients were classified into conservative management, antithrombotics change, and induced hypertension (iHTN). The primary outcomes were neurological improvement, defined as a ≥2-point reduction in the National Institutes of Health Stroke Scale score, and 3-month functional outcome measured by modified Rankin Scale ordinal shift. Secondary outcomes included good functional recovery (modified Rankin Scale score, 0–2) and composite vascular events (death, stroke, and myocardial infarction). Multivariable analyses adjusted for age, sex, prestroke modified Rankin Scale, initial National Institutes of Health Stroke Scale score, vascular risk factors, the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, acute thrombolysis, and laboratory covariates.

RESULTS: Among 3067 patients with END due to stroke progression, 1840 (60.0%) received conservative management, 747 (24.4%) underwent antithrombotic changes, and 480 (15.7%) were treated with iHTN. Neurological improvement occurred in 34.2% of patients, with the highest in the iHTN group (41.5%) compared with the conservative (32.2%) and antithrombotics change groups (34.4%; $P<0.001$). In adjusted analyses, iHTN increased the odds of neurological improvement (adjusted odds ratio, 1.55 [95% CI, 1.25–1.92]) and a favorable 3-month modified Rankin Scale shift (adjusted odds ratio, 1.24 95% CI, 1.03–1.48]) compared with conservative management, particularly in patients with large artery atherosclerosis. Antithrombotics change showed no significant association with neurological or functional recovery.

CONCLUSIONS: In patients with noncardioembolic ischemic stroke who developed END due to stroke progression, iHTN was associated with favorable clinical outcomes.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: fibrinolytic agents ■ hypertension ■ ischemic attack, transient ■ ischemic stroke ■ thrombosis

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.125.053320.
For Sources of Funding and Disclosures, see page XXX.

Stroke is available at www.ahajournals.org/journal/str

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Nonstandard Abbreviations and Acronyms

aOR	adjusted odds ratio
CRCS-K	Clinical Research Collaboration for Stroke-Korea
END	early neurological deterioration
HR	hazard ratio
iHTN	induced hypertension
LAA	large artery atherosclerosis
mRS	modified Rankin Scale
NI	neurological improvement
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
SVO	small vessel occlusion
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Early neurological deterioration (END) occurs in ≈10% to 40% of patients during the acute ischemic stroke and is strongly associated with prolonged hospitalization, long-term disability, and increased mortality.[1–4] Despite its clinical importance, treatment strategies for END remain largely empiric. In current practice, management decisions are often based on individual clinician preference rather than standardized guidelines, resulting in considerable variability in care.[5,6] Moreover, there is a notable lack of high-quality evidence comparing the effectiveness of different treatment approaches, highlighting the need for systematic investigation.

When systemic medical causes are excluded, END is commonly attributed to stroke progression, recurrence of stroke, symptomatic hemorrhagic transformation, or malignant edema, with stroke progression being the most frequent cause.[5,7,8] END due to stroke progression is typically driven by infarct expansion or perilesional edema due to hypoperfusion or thrombus propagation.[8,9] Based on this pathophysiology, treatment strategies such as induced hypertension (iHTN) or the intensification of antithrombotic therapy have been proposed to augment cerebral perfusion and potentially confer neuroprotective benefits.

Although limited studies suggest that these strategies may improve neurological outcomes in patients with END,[10–12] their clinical application remains inconsistent, and clear guidance, particularly in the context of noncardioembolic stroke, is lacking. Most importantly, the comparative effectiveness of these different treatment approaches has not been systematically assessed in real-world practice.

Therefore, this study aimed to address this evidence gap by focusing on patients with noncardioembolic ischemic stroke who develop END due to stroke progression. We investigate the real-world practice of 3 commonly applied management strategies, conservative treatment, change in antithrombotic therapy, and iHTN, and compare their associations with early neurological improvement (NI) during hospitalization and functional outcomes at 3 months.

METHODS

Data Availability

The data used in this study are available upon reasonable request following the submission of a legitimate academic research proposal to be assessed by the Clinical Research Collaboration for Stroke-Korea (CRCS-K) Steering Committee. One may request to contact the corresponding author regarding data availability.

Study Design and Subjects

This study was conducted using data from the CRCS-K registry, a prospective, multicenter, nationwide, Web-based database that includes consecutive patients with acute stroke or transient ischemic attack admitted to 20 academic hospitals across South Korea. Detailed information on the CRCS-K registry has been reported previously.[13,14] Regular monitoring and systematic audits were performed to ensure and enhance data quality. Prospective collection of information on END management began in January 2019.

Eligible patients met the following criteria: (1) admission for an acute cerebrovascular event between January 2019 and August 2024; (2) a diagnosis of acute ischemic stroke or transient ischemic attack within 7 days of symptom onset; (3) classification as having noncardioembolic stroke according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria[15]; (4) documented occurrence of END during hospitalization; and (5) END specifically attributed to stroke progression. Patients were excluded if END was due to symptomatic hemorrhagic transformation, malignant cerebral edema, or other nonischemic causes. In addition, cases were excluded if END management involved intracranial pressure control (eg, hyperosmolar therapy, decompressive craniectomy, or hypothermia), reperfusion therapy, or bypass surgery. The flowchart of the study is presented in Figure S1.

This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Definition of END and Subtypes

END was defined as any new neurological symptoms or worsening of neurological status meeting at least 1 of the following criteria: (1) an increase in the total National Institutes of Health Stroke Scale (NIHSS) score by >2 points; (2) an increase in the NIHSS subscore for level of consciousness by >1 point; or (3) an increase in the NIHSS subscore for motor function by >1 point. These changes had to occur during hospitalization due to the index stroke and within 3 weeks of symptom onset.[16,17]

In our study, we included patients with END attributable to stroke progression, as this is the most frequent mechanism of END and represents a potentially modifiable target for therapeutic intervention.[8] END attributable to stroke

progression was defined as deterioration caused by progressive ischemia, swelling of the infarcted tissue, or perilesional edema in the initially affected vascular territory, as confirmed on follow-up imaging. The neurological worsening had to persist for more than 24 hours. We used an END cohort previously described in the literature, where neurological worsening due to nonvascular causes (eg, seizures, infections, or medical complications) was systematically categorized separately and excluded from the definition of END applied in this study.[8]

END Management

END management strategies were classified into 3 categories. The conservative group included patients who continued preexisting medications without change, underwent dose reductions or discontinuation, or received intravascular volume expansion after the onset of END. The antithrombotics change group comprised patients with whom antithrombotic therapy was modified after the occurrence of END. This included switching to a different combination of oral antiplatelet regimen, adding additional medication to the ongoing antithrombotic therapy, or initiating parenteral anticoagulants or antithrombotics such as direct thrombin inhibitors or glycoprotein IIb/IIIa inhibitors. The iHTN group was defined as those who received intravenous vasopressors to raise systolic blood pressure, generally by 10% to 20% above baseline levels, according to each participating center's protocol, which was informed by prior studies.[11] In South Korea, there are currently no standardized guideline recommendations for the management of END. The use of various treatment strategies, including iHTN, was determined at the discretion of each treating physician and participating center.

Data Collection

Demographic, clinical, and laboratory data were collected prospectively. NIHSS scores were assessed at admission by the attending physician and re-evaluated by the stroke physician or stroke team whenever neurological changes were observed. Stroke subtypes were classified according to the TOAST criteria as large artery atherosclerosis (LAA), small vessel occlusion (SVO), undetermined cause, or other determined cause.[15] The classification of ischemic stroke subtypes was based on magnetic resonance imaging–based algorithms.[18] The modified Rankin Scale (mRS) score and poststroke vascular events (stroke, myocardial infarction, and death) were prospectively assessed at 3 months after discharge by physicians and nurses at participating centers who were trained and certified in a standardized manner through a Web-based education system. Structured clinic visits or telephone interviews were conducted according to the predefined protocol. Regular on-site audits and data monitoring by the outcome adjudication committee ensured data quality and intercenter consistency. A detailed description of these standardized assessment procedures has been reported previously.[13,14] To further examine the robustness of our findings, subgroup analyses were performed for the primary outcomes according to baseline characteristics that could plausibly influence treatment selection or outcomes, including age (<70 versus ≥70 years), the presence of hypertension, the presence of coronary heart disease, and baseline NIHSS score (≤4 versus >4).

Outcome

The primary outcomes were (1) NI, defined as an improvement of >2 points in the NIHSS score between the time of END and discharge and (2) the 3-month functional outcome assessed using an ordinal shift analysis of the mRS. Secondary outcomes included good functional outcome at 3 months (defined as mRS score, 0–2), composite vascular outcome comprising stroke recurrence, myocardial infarction, and all-cause death, as well as the individual components of this composite outcome. Subgroup analyses of the primary outcomes were also performed according to the TOAST classification.

Ethic Statement

Clinical information was collected from the CRCS-K registry with approval from the local institutional review boards of all participating centers. A waiver for informed consent was provided because of study subject anonymity and minimal risk to the participants. The current study was approved by local institutional review boards at all participating centers, including Chonnam National University Hospital (CNUH-2025-234).

Statistical Analysis

Baseline characteristics and outcomes were compared among the different END management groups using the χ^2 test, the ANOVA, or the Kruskal-Wallis test, as appropriate for the type of variable. The following parameters had missing data that were substituted using median values: hemoglobin (0.03%), low-density lipoprotein (0.5%), and glycated hemoglobin (1.0%). The event probabilities of NI during hospitalization, ordinal shift in mRS scores at 3 months, good functional outcome (mRS score, 0–2), and 3-month vascular outcomes were estimated using the Kaplan-Meier method, and differences among the groups were assessed using the log-rank test. These analyses were performed both in the overall cohort and within subgroups based on stroke subtype.

Odds ratios (ORs) or hazard ratios (HRs) with 95% CIs were calculated for the following outcomes: NI during hospitalization, ordinal shift in the mRS score at 3 months, good functional outcome (mRS score, 0–2), and 3-month vascular outcomes. Binary logistic regression analysis was used for NI and good functional outcome, while ordinal logistic regression was applied for the analysis of mRS shift. The Cox proportional hazards model was used to evaluate 3-month vascular outcomes. All analyses were performed separately for each END management group. Covariate adjustments included age, sex, prestroke mRS, initial NIHSS, comorbidities (history of hypertension, diabetes, prior stroke, dyslipidemia, and coronary heart disease), TOAST classification, acute thrombolytic therapy, and any variables with a P value <0.1 in baseline comparisons.

Two-sided P<0.05 was considered statistically significant. All statistical analyses were conducted using R software with the rms package (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria) and SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

General Characteristics

The mean follow-up duration of patients was 90.7±7.8 days. A total of 3067 patients (age, 70.0±13.0 years;

male, 58.0%) with END due to stroke progression were included in the analysis. Of these, 1840 (60.0%) were managed conservatively, 747 (24.4%) underwent antithrombotic changes, and 480 (15.7%) were treated with iHTN. The median NIHSS score was 4 (2–6) at admission, 7 (4–9) at the time of END, and 6 (3–9) at discharge. According to the TOAST classification, LAA was the most frequent subtype, accounting for 54.5% of patients (n=1670).

Across the treatment groups, the antithrombotic change group had a lower NIHSS score at admission (median, 3 [2–6]) compared with the conservative group (4, [2–7]) and the iHTN group (4, [2–6]; *P*<0.001). The history of hypertension was more common in the conservative (71.7%) and antithrombotic change (71.1%) groups, and less common in the iHTN group (59.4%; *P*<0.001). Coronary heart disease was most prevalent in the conservative group (9.4%) and least in the iHTN group (4.0%; *P*<0.001). The iHTN group had the highest proportion of LAA subtype (64.0%; *P*<0.001). Acute reperfusion therapy was most frequently performed in the conservative group (18.2%; *P*<0.001; Table 1).

Primary Outcomes

Among the total study population, 1049 (34.2% [95% CI, 32.5–35.9]) achieved NI. The proportion of patients with NI was 32.2% (95% CI, 30.1–34.4) in the conservative group, 34.4% (95% CI, 31.0–37.9) in the antithrombotic change group, and 41.5% (95% CI, 37.0–46.0) in the iHTN group, with differences observed among groups (*P*<0.001). While the median 3-month mRS score was similar across groups (3 [interquartile range, 2–4]), the overall distribution differed (*P*<0.001; Table 2).

In the crude analysis, patients in the iHTN group were more likely to achieve NI compared with those in the conservative group (OR, 1.49 [95% CI, 1.21–1.83]) and also showed greater improvement in functional outcomes (OR, 1.55 [95% CI, 1.30–1.84]). The antithrombotic change group did not show an association with NI but was associated with improved functional outcomes (OR, 1.28 [95% CI, 1.10–1.48]). After adjustment for potential confounders, only the iHTN group remained significantly associated with increased odds of NI (adjusted OR [aOR], 1.55 [95% CI, 1.25–1.92]) and a favorable functional outcome shift (aOR, 1.24 [95% CI, 1.03–1.48]) compared with the conservative group (Table 3). Groupwise differences in mRS distributions are illustrated in Figure 1.

Secondary Outcomes

Overall, 1134 (37.0% [95% CI, 35.3–38.7]) of patients achieved a good functional outcome (mRS score, 0–2) at 3 months. The iHTN group had the highest rate at 42.1% (95% CI, 37.6–46.6), with a difference observed across treatment groups (*P*=0.015; Table 2). In crude analysis, patients in the iHTN group were more likely to achieve a good functional outcome compared with conservative management (OR, 1.34 [95% CI, 1.09–1.64]), but this association was not statistically significant after multivariable adjustment (aOR, 1.17 [95% CI, 0.92–1.48]; Table 3).

Composite vascular events within 3 months occurred in 294 (9.7% [95% CI, 8.6%–10.7%]) of all patients, with event rates of 11.3% (95% CI, 9.8%–12.7%) in the conservative group, 8.2% (95% CI, 6.3%–10.2%) in the antithrombotic change group, and 5.9% (95% CI, 3.8%–8.0%) in the iHTN group, showing a difference among groups (*P*<0.001). Overall mortality was 6.5% (95% CI, 5.6%–7.3%), with event rates of 8.1% (95% CI, 6.9%–9.4%) in the conservative group, 4.8% (95% CI, 3.3%–6.4%) in the antithrombotic change group, and 2.6% (95% CI, 1.1%–4.0%) in the iHTN group (*P*<0.001). The incidence of recurrent stroke and myocardial infarction was low across all groups, with no differences observed (Table 2).

In the crude analysis, both the antithrombotic change group (HR, 0.72 [95% CI, 0.54–0.96]) and the iHTN group (HR, 0.51 [95% CI, 0.34–0.76]) were associated with a lower risk of composite vascular events compared with the conservative group. Similarly, both the antithrombotic change group (HR, 0.57 [95% CI, 0.40–0.83]) and the iHTN group (HR, 0.30 [95% CI, 0.17–0.55]) were associated with reduced mortality risk. However, after multivariable adjustment, iHTN was associated with a lower risk of mortality (adjusted HR, 0.50 [95% CI, 0.28–0.92]), whereas no significant association was observed in composite vascular events (adjusted HR, 0.67 [95% CI, 0.45–1.01]). In the antithrombotic change group, the risk differences observed in the crude analysis were no longer evident after adjustment for confounders (Table 4). Survival curves for vascular outcomes are presented in Figure 2.

Outcomes According to TOAST Classification

In patients with LAA (n=1670), the iHTN group showed higher rates of good mRS score (0–2) at 3 months (42.0% versus 31.1%; *P*=0.002) and NI (41.4% versus 31.9%; *P*=0.007) compared with the conservative group. For those with SVO (n=604), the proportion of NI was higher in the iHTN group (42.7% [95% CI, 33.3%–52.5%]) compared with the conservative (28.9% [95% CI, 24.1%–34.0%]) and antithrombotic change groups (30.4% [95% CI, 23.3%–38.2%]). However, there was no difference in the proportion of patients achieving a good functional outcome at 3 months across the treatment groups. Among patients with undetermined cause or other determined cause (n=793), neither NI

Table 1. General Characteristics According to END Management

Variable	Total	Conservative	Antithrombotics change	iHTN	*P* value
Number	3067	1840 (60.0%)	747 (24.4%)	480 (15.7%)	
Age, y; mean±SD	70.0±13.0	70.2±13.1	69.7±13.0	69.6±12.2	0.560
Male, n (%)	1778 (58.0)	1087 (59.1)	417 (55.8)	274 (57.1)	0.288
Initial NIHSS, median (IQR)	4 (2–6)	4 (2–7)	3 (2–6)	4 (2–6)	<0.001
NIHSS score at END, median (IQR)	7 (4–9)	7 (4–10)	6 (4–9)	7 (5–9)	0.001
Discharge NIHSS score, median (IQR)	6 (3–9)	6 (3–9)	5 (3–8)	5 (3–8)	<0.001
Prestroke mRS score, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	<0.001
History of TIA, n (%)	48 (1.6)	28 (1.5)	13 (1.7)	7 (1.5)	0.902
History of stroke, n (%)	593 (19.3)	365 (19.8)	144 (19.3)	84 (17.5)	0.513
History of CHD, n (%)	254 (8.3)	173 (9.4)	62 (8.3)	19 (4.0)	<0.001
History of HTN, n (%)	2136 (69.6)	1320 (71.7)	531 (71.1)	285 (59.4)	<0.001
History of DM, n (%)	1206 (39.3)	746 (40.5)	288 (38.6)	172 (35.8)	0.151
History of dyslipidemia, n (%)	1165 (38.0)	726 (39.5)	271 (36.3)	168 (35.0)	0.109
Smoking, n (%)					0.328
None	2054 (67.0)	1223 (66.5)	510 (68.3)	321 (66.9)	
Current	722 (23.5)	429 (23.3)	170 (22.8)	123 (25.6)	
Ex-smoking	291 (9.5)	188 (10.2)	67 (9.0)	36 (7.5)	
History of antiplatelet, n (%)	791 (25.8)	483 (26.3)	198 (26.5)	110 (22.9)	0.290
History of HTN medication, n (%)	1551 (50.6)	956 (52.0)	376 (50.3)	219 (45.6)	0.047
History of statin medication, n (%)	750 (24.5)	464 (25.2)	166 (22.2)	120 (25.0)	0.263
History of other lipid med, n (%)	135 (4.4)	82 (4.5)	34 (4.6)	19 (4.0)	0.871
History of DM medication, n (%)	865 (28.2)	533 (29.0)	202 (27.0)	130 (27.1)	0.515
TOAST, n (%)					<0.001
LAA	1670 (54.5)	975 (53.0)	388 (51.9)	307 (64.0)	
SVO	604 (19.7)	336 (18.3)	158 (21.2)	110 (22.9)	
UD	151 (4.9)	112 (6.1)	27 (3.6)	12 (2.5)	
OD	642 (20.9)	417 (22.7)	174 (23.3)	51 (10.6)	
Acute treatment, n (%)					<0.001
None	2584 (84.3)	1506 (81.8)	651 (87.1)	427 (89.0)	
IVT	291 (9.5)	191 (10.4)	66 (8.8)	34 (7.1)	
IAT	137 (4.5)	102 (5.5)	21 (2.8)	14 (2.9)	
IVT+IAT	55 (1.8)	41 (2.2)	9 (1.2)	5 (1.0)	
Laboratory, mean±SD					
WBC	8.2±3.1	8.3±3.2	8.1±2.9	7.9±2.7	0.010
Hemoglobin	13.7±1.9	13.7±1.9	13.7±1.9	13.8±1.7	0.499
Platelet	233.2±71.1	232.0±71.7	235.1±71.8	234.9±67.7	0.519
Creatinine	0.97±0.80	0.99±0.85	1.00±0.86	0.88±0.36	0.014
Fasting glucose	131.6±53.6	132.7±54.8	134.4±55.2	122.9±44.8	<0.001
LDL-C	113.2±41.6	113.0±42.4	113.6±39.2	113.5±41.9	0.923
HbA1c	6.5±1.5	6.5±1.6	6.5±1.6	6.4±1.3	0.131
SBP	160.2±29.1	160.6±30.1	159.0±28.1	160.5±26.8	0.430

P values are calculated by the χ^2 test, the ANOVA, and the Kruskal-Wallis Test. CHD indicates coronary heart disease; DM, diabetes; END, early neurological deterioration; HbA1c, glycated hemoglobin; HTN, hypertension; IAT, intra-arterial thrombectomy; iHTN, induced hypertension; IQR, interquartile range; IVT, intravenous thrombolysis; LAA, large artery atherosclerosis; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OD, other cause; SBP, systolic blood pressure; SVO, small vessel occlusion; TIA, transient cerebral ischemia; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UD, undetermined cause; and WBC, white blood cell.

nor 3-month functional outcomes differed significantly between treatment strategies. The rate of composite vascular events was lower in the iHTN group (4.8% [95% CI, 0%–10.1%]) compared with the conservative (16.7% [95% CI, 13.5%–19.9%]) and antithrombotic change groups (11.1% [95% CI, 6.7%–15.5%]; Table 5).

Table 2. Event Rate of Primary and Secondary Outcomes According to END Management

	All	Conservative	Antithrombotics change	iHTN	*P* value
Neurological improvement during hospitalization (NIHSS score improvement ≥2)					
No. of events	1049	593	257	199	
Event rate, % (95% CI)	34.2 (32.5–35.9)	32.2 (30.1–34.4)	34.4 (31.0–37.9)	41.5 (37.0–46.0)	<0.001
Ordinal shift for 3-mo mRS score*					
Median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	<0.001
Good functional outcome at 3 mo (mRS score, 0–2)					
No. of events	1134	647	285	202	
Event rate, % (95% CI)	37.0 (35.3–38.7)	35.2 (33.0–37.4)	38.2 (34.7–41.7)	42.1 (37.6–46.6)	0.015
Composite vascular events (including all-cause mortality, recurrent stroke, and myocardial infarction)					
No. of events	294	205	61	28	
Event rate, % (95% CI)	9.7 (8.6–10.7)	11.3 (9.8–12.7)	8.2 (6.3–10.2)	5.9 (3.8–8.0)	<0.001
All-cause mortality					
No. of events	194	147	35	12	
Event rate, % (95% CI)	6.5 (5.6–7.3)	8.1 (6.9–9.4)	4.8 (3.3–6.4)	2.6 (1.1–4.0)	<0.001
Stroke recurrence					
No. of events	89	51	23	15	
Event rate, % (95% CI)	3.0 (2.4–3.6)	2.9 (2.1–3.7)	3.2 (1.9–4.4)	3.2 (1.6–4.7)	0.911
Myocardial infarction					
No. of events	32	23	8	1	
Event rate, % (95% CI)	1.1 (0.7–1.4)	1.3 (0.8–1.8)	1.1 (0.3–1.8)	0.2 (0.0–0.6)	0.133

Adjusted variables: male, age, initial NIHSS score, prestroke mRS score (0–1), history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of dyslipidemia, treatment history of hypertension, TOAST classification, acute reperfusion therapy, WBC, creatinine, and fasting glucose level. END indicates early neurological deterioration; iHTN, induced hypertension; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and WBC, white blood cell.

*The ordinal shift across the range of mRS scores toward a better outcome, for which the treatment effect is reported as a common OR with the 95% CI.

In patients with LAA, iHTN was associated with NI compared with the conservative group (aOR, 1.57 [95% CI, 1.19–2.06]), as well as with greater odds of achieving a favorable mRS shift (aOR, 1.46 [95% CI, 1.16–1.84]) and good functional outcome at 3 months (aOR, 1.40 [95% CI, 1.03–1.89]). Among patients with SVO, iHTN was also associated with NI (aOR, 1.88 [95% CI, 1.16–3.05]) but not with functional outcomes. Among patients with undetermined cause or other determined cause, no significant associations were observed between treatment strategy and 3-month functional outcomes (Table 6).

Subgroup Analysis

Subgroup analyses were conducted for the 3-month mRS ordinal shift (Table S1; Figure S2) and NI (Table S2; Figure S3). Overall, iHTN tended to be associated with more favorable outcomes across subgroups. For the mRS ordinal shift, the beneficial effect of iHTN did not differ according to baseline hypertension ($P_{interaction}$=0.865) or coronary heart disease ($P_{interaction}$=0.550), indicating that the association was consistent regardless of these comorbidities. In contrast, a significant interaction was observed for baseline NIHSS severity ($P_{interaction}$=0.029), suggesting that the magnitude of the effect may vary by initial stroke severity. Nevertheless, iHTN was associated with a favorable direction of outcome compared with other treatment strategies in both subgroups (NIHSS score ≤4 and >4). For NI, no significant interactions were observed with any of the tested variables.

DISCUSSION

In this nationwide study using the CRCS-K registry, we analyzed over 3000 patients with END attributed to stroke progression. Among these patients, approximately one-quarter underwent changes in antithrombotic therapy, and iHTN was implemented in about 15% of patients with END. Compared with conservative management, iHTN was significantly associated with greater improvement in NIHSS scores at discharge and a favorable shift in the 3-month mRS distribution. These associations were particularly evident in patients with the LAA subtype. Our findings suggest that iHTN may offer potential clinical benefit in the management of progressive END and provide a basis for hypothesis generation and future prospective investigations.

Although prior research has addressed END management, real-world treatment approaches remain

Table 3. Clinical Outcomes According to END Management

	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Primary outcomes				
Neurological improvement during hospitalization (NIHSS score improvement ≥2)				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	1.10 (0.92–1.32)	0.286	1.17 (0.97–1.40)	0.964
Induced hypertension	1.49 (1.21–1.83)	<0.001	1.55 (1.25–1.92)	<0.001
Ordinal shift for 3-mo mRS score*				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	1.28 (1.10–1.48)	0.001	1.02 (0.87–1.19)	0.809
Induced hypertension	1.55 (1.30–1.84)	<0.001	1.24 (1.03–1.48)	0.023
Secondary outcomes				
Good functional outcome at 3 mo (mRS score, 0–2)				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	1.14 (0.95–1.36)	0.151	0.97 (0.79–1.19)	0.760
Induced hypertension	1.34 (1.09–1.64)	0.005	1.17 (0.92–1.48)	0.197

Adjusted variables: male, age, initial NIHSS score, prestroke mRS score (0–1), history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of dyslipidemia, treatment history of hypertension, TOAST classification, acute reperfusion therapy, WBC, creatinine, and fasting glucose level. END indicates early neurological deterioration; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odd ratio; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and WBC, white blood cell.

*The ordinal shift across the range of mRS scores toward a better outcome, for which the treatment effect is reported as a common OR with the 95% CI.

heterogeneous and lack clearly defined standards.[5] In our registry-based analysis reflecting real-world clinical practice, ≈60% of patients with END were managed conservatively, including approaches such as volume expansion. This likely reflects the complex and heterogeneous mechanisms underlying progressive END, as well as the absence of established efficacy for specific treatment strategies in previous studies.[9,19] In this challenging clinical context, our findings provide supporting evidence for the potential benefit of selecting treatment strategies, as certain approaches were associated with better outcomes.

In our study, iHTN was implemented in ≈15% of patients with END following noncardioembolic stroke, indicating its relatively infrequent use in clinical practice. However, compared with conservative management, iHTN was associated with a 55% higher likelihood of achieving NI and a 24% greater likelihood of a favorable shift in functional outcome at 3 months. Given the significant associations between iHTN and the primary outcomes, NI and mRS shift, iHTN may be more favorably associated with overall neurological recovery after END. These results support a previous randomized clinical trial conducted in patients who developed END following ischemic stroke due to LAA or SVO.[11] In that trial, iHTN increased the likelihood of achieving NI (defined as a ≥2-point improvement in NIHSS) by 57% and functional independence at 3 months by 75% compared with placebo. A subgroup analysis showed that these effects were particularly pronounced in patients with SVO. Unlike previous studies, we found that iHTN was associated with better outcomes in patients with LAA within this cohort. Furthermore, because we focused on post-END management and excluded patients who underwent EVT after END, these findings suggest that iHTN may represent a potential therapeutic option for patients with LAA with END in whom EVT is not feasible. Notably, despite higher initial NIHSS scores, the iHTN group had ≈50% lower mortality compared with other treatment strategies, addressing previous safety concerns such as thrombus propagation or hemorrhagic transformation.[20] By contrast, although iHTN was associated with NIHSS score improvement in patients with SVO, this did not lead to better functional outcomes, possibly due to the higher baseline severity in our study; only 37.0% achieved a good functional outcome at 3 months.

In clinical practice, changes in antiplatelet or antithrombotic therapy, including intravenous agents, are often considered after END although evidence remains limited. In our study, antithrombotic therapy was modified in approximately a quarter of patients after END. Compared with conservative management, the antithrombotic change group was not significantly associated with either NI or improved functional outcomes. This may be due to the substantial heterogeneity of the group, which included a wide range of therapeutic approaches, making it difficult to isolate the effect of any single antithrombotic intervention. Accordingly, further studies are warranted to evaluate the efficacy of specific, clearly defined antithrombotic strategies in the management of END.

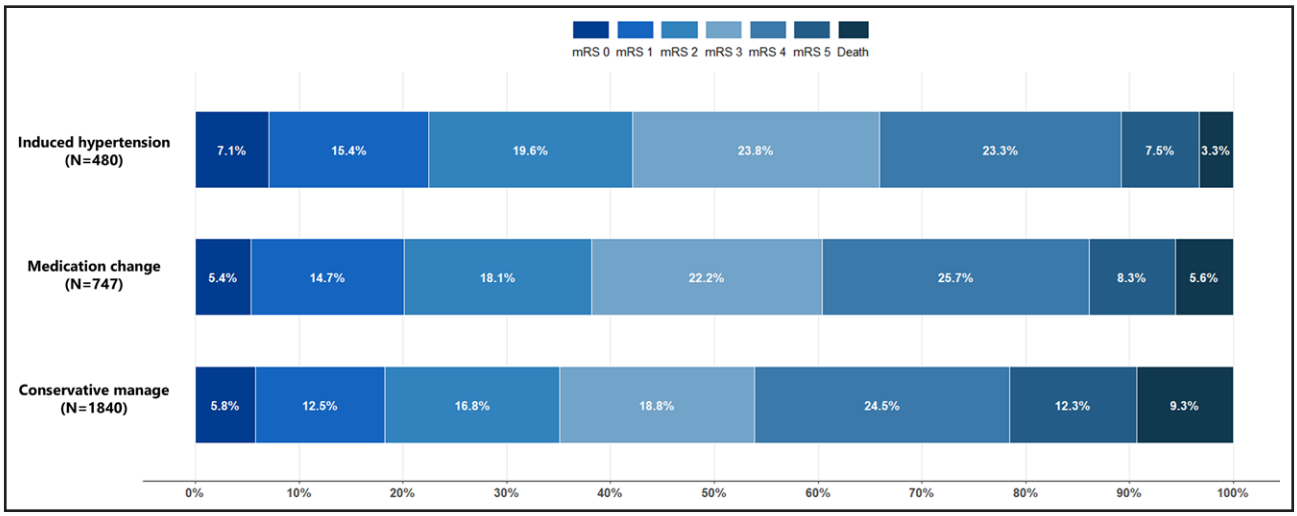

Figure 1. Modified Rankin Scale (mRS) distribution at 3 months according to early neurological deterioration management.

In a previous study involving predominantly LAA and SVO subtypes, intravenous argatroban administered after END was associated with a modest benefit for good functional outcome at 3 months (risk ratio, 1.10 [95% CI, 1.00–1.20]). However, interpretation of these results is limited due to the use of a broad outcome definition (mRS score, 0–3).[10] Tirofiban has also been reported to yield better outcomes than aspirin in patients without large or medium vessel occlusion.[12] In that study, 40.2% of patients had END or stroke progression, suggesting possible relevance, although the effect of tirofiban in the END-specific subgroup was not clearly demonstrated. Intravenous antithrombotic agents have been explored as potential strategies following END; however, clear evidence supporting their efficacy remains limited. Further studies are needed to clarify the role of specific antithrombotic strategies in the management of END. Although dual-antiplatelet therapy is the standard treatment in the acute phase of ischemic stroke,[21] some clinicians have attempted to add a third agent after END. However, triple-antiplatelet therapy increases the risk of bleeding without improving clinical outcomes.[22]

Our findings provide clinical insight into the management of END, for which treatment strategies remain

Table 4. Vascular Outcomes According to END Management

	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Composite vascular events (including all-cause mortality, recurrent stroke, and myocardial infarction)				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	0.72 (0.54–0.96)	0.025	0.87 (0.65–1.16)	0.348
Induced hypertension	0.51 (0.34–0.76)	<0.001	0.67 (0.45–1.01)	0.055
All-cause mortality				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	0.57 (0.40–0.83)	0.003	0.79 (0.54–1.13)	0.188
Induced hypertension	0.30 (0.17–0.55)	<0.001	0.50 (0.28–0.92)	0.024
Stroke recurrence				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	1.09 (0.67–1.79)	0.725	1.08 (0.66–1.78)	0.750
Induced hypertension	1.10 (0.62–1.96)	0.738	1.10 (0.61–1.98)	0.759
Myocardial infarction				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	0.85 (0.38–1.90)	0.693	0.93 (0.41–2.09)	0.853
Induced hypertension	0.16 (0.02–1.22)	0.077	0.16 (0.02–1.19)	0.072

Adjusted variables: male, age, initial NIHSS score, prestroke mRS score (0–1), history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of dyslipidemia, treatment history of hypertension, TOAST classification, acute reperfusion therapy, WBC, creatinine, and fasting glucose level. END indicates early neurological deterioration; HR, hazard ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and WBC, white blood cell.

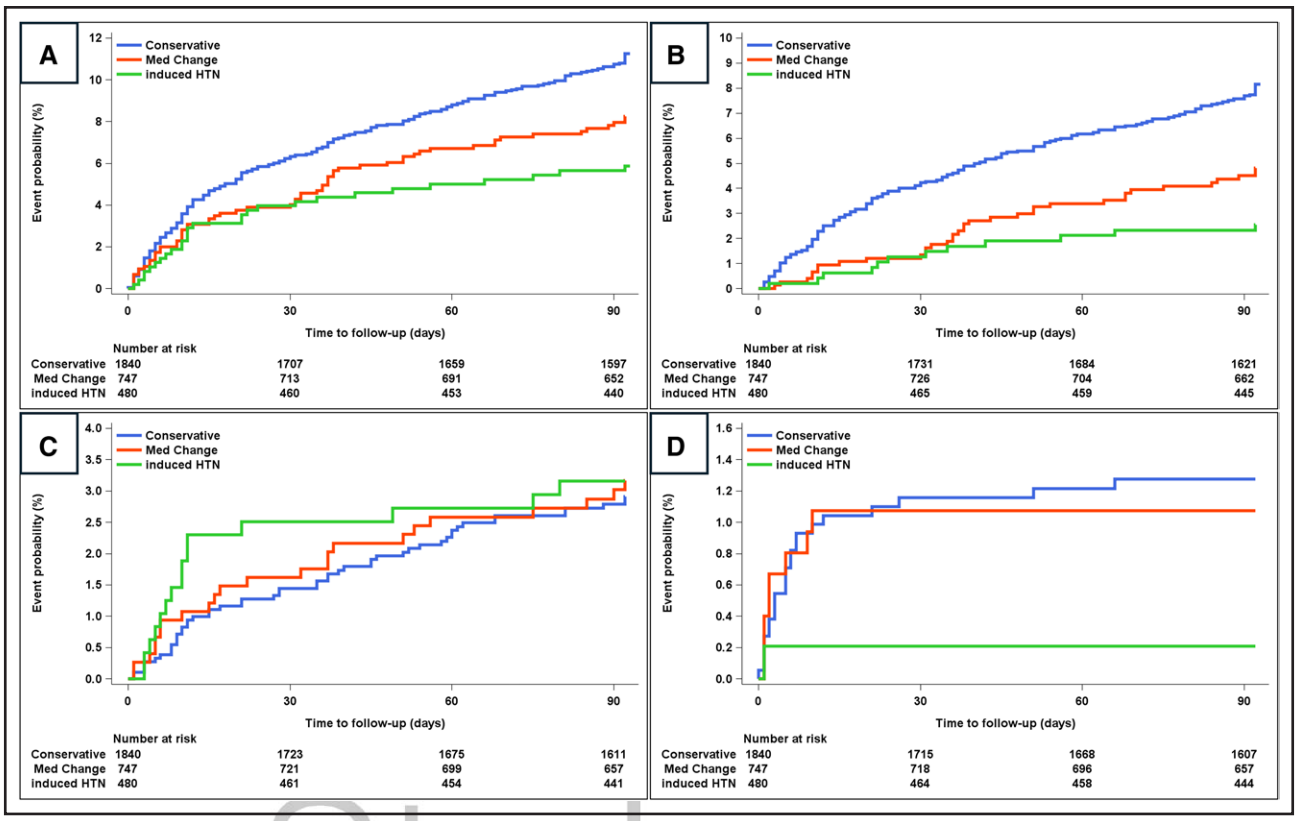

Figure 2. Survival curve for 3-month vascular outcome.
A, Composite vascular outcome. **B**, All-cause mortality. **C**, Stroke. **D**, Myocardial infarction. HTN indicates hypertension.

largely undefined. In particular, we observed a favorable association between iHTN and improved outcomes in patients with END, suggesting that more proactive interventions may be beneficial in progressive END. Although our study was not specifically designed to define which patients should or should not receive iHTN, the TOAST subgroup analyses yielded clinically meaningful signals. Patients with END due to LAA appeared to experience both neurological and functional benefits, suggesting that this subgroup may be more likely to respond favorably. However, these findings should not be interpreted as a recommendation to uniformly increase blood pressure in all patients with END. While several studies have reported on the safety of iHTN after END, some have also raised concerns that the risk of complications such as intracerebral hemorrhage may increase.[20,23,24] The potential benefits of iHTN are likely to depend on baseline hemodynamic status and individual patient characteristics, underscoring the need for a tailored rather than a one-size-fits-all approach.

Table 5. Event Rates According to TOAST Classification

Stroke subtype	Outcome	Conservative	Antithrombotics change	Induced hypertension	*P* value
LAA (n=1670)	Good mRS score at 3-mo (0–2) event rate, % (95% CI)	31.1 (28.2–34.1)	34.5 (29.8–39.5)	42.0 (36.4–47.8)	0.002
	Improvement of NIHSS ≥2 event rate, % (95% CI)	31.9 (29.0–34.9)	36.3 (31.5–41.3)	41.4 (35.8–47.1)	0.007
	Composite vascular outcome event rate, % (95% CI)	11.4 (9.4–13.4)	8.5 5.7–11.3)	7.2 (4.3–10.1)	0.066
SVO (n=604)	Good mRS score at 3-mo (0–2) event rate, % (95% CI)	48.5 (43.1–54.0)	44.3 (36.4–52.4)	47.3 (37.7–57.0)	0.682
	Improvement of NIHSS ≥2 event rate, % (95% CI)	28.9 (24.1–34.0)	30.4 (23.3–38.2)	42.7 (33.3–52.5)	0.023
	Composite vascular outcome event rate, % (95% CI)	2.4 (0.8–4.0)	3.9 (0.8–7.0)	2.8 (0.0–5.8)	0.648
UD+OD (n=793)	Good mRS score at 3-mo (0–2) event rate, % (95% CI)	34.2 (30.2–38.4)	30.8 (24.5–37.7)	33.3 (22.0–46.3)	0.689
	Improvement of NIHSS ≥2 event rate, % (95% CI)	35.0 (30.9–39.2)	33.8 (27.3–40.8)	39.7 (27.6–52.8)	0.695
	Composite vascular outcome event rate, % (95% CI)	16.7 (13.5–19.9)	11.1 (6.7–15.5)	4.8 (0.0–10.1)	0.014

P values are calculated by the χ^2 test and the log-rank test. END indicates early neurological deterioration; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OD, other cause; SVO, small vessel occlusion; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and UD, undetermined cause.

Table 6. Clinical Outcomes According to TOAST Classification

Subtype	Group	Ordinal shift for good mRS score*	*P* value	Good mRS score at 3 mo (0–2)	*P* valu	NIHSS score improvement (≥2)	*P* value
LAA (n=1670)	Conservative management	1 (Ref)		1 (Ref)		1 (Ref)	
	Antithrombotics change	1.16 (0.93–1.43)	0.184	1.15 (0.87–1.52)	0.338	1.26 (0.78–1.62)	0.071
	Induced hypertension	1.46 (1.16–1.84)	0.002	1.40 (1.03–1.89)	0.030	1.57 (1.19–2.06)	0.001
SVO (n=604)	Conservative management	1 (Ref)		1 (Ref)		1 (Ref)	
	Antithrombotics change	0.90 (0.64–1.28)	0.557	0.91 (0.59–1.41)	0.676	1.08 (0.69–1.68)	0.72
	Induced hypertension	1.12 (0.75–1.67)	0.594	1.08 (0.651–1.78)	0.774	1.88 (1.16–3.05)	0.009
UD+OD (n=793)	Conservative management	1 (Ref)		1 (Ref)		1 (Ref)	
	Antithrombotics change	0.85 (0.63–1.14)	0.282	0.74 (0.49–1.10)	0.139	1.03 (0.72–1.47)	0.867
	Induced hypertension	0.84 (0.53–1.34)	0.469	0.66 (0.35–1.24)	0.204	1.20 (0.69–2.09)	0.509

Adjusted variables: male, age, initial NIHSS score, prestroke mRS score (0–1), history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of dyslipidemia, treatment history of hypertension, TOAST classification, acute reperfusion therapy, WBC, creatinine, and fasting glucose level. END indicates early neurological deterioration; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OD, other cause; OR, odds ratio; SVO, small vessel occlusion; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UD, undetermined cause; and WBC, white blood cell.

*The ordinal shift across the range of mRS scores toward a better outcome, for which the treatment effect is reported as a common OR with the 95% CI.

While conservative management remains prevalent in clinical practice, our findings underscore the urgent need for evidence-based guidelines to inform treatment decisions following END. To date, previous studies have focused on identifying risk factors for END[25,26] and exploring various preventive strategies to reduce its occurrence.[27–33] While these efforts have emphasized prevention, our study focused on therapeutic approaches after the onset of END. Moving forward, a comprehensive approach that includes early risk stratification, prevention, and timely intervention will be essential to improving outcomes in patients at risk of END.

This study has several limitations. First, due to its retrospective observational study design, the possibility of residual confounding cannot be entirely excluded, despite adjustment for multiple potential covariates. Second, detailed information on emerging acute-phase treatments intended to prevent END was not available. Although such therapies may have influenced outcomes, they are still supported by limited evidence, and their use is likely to have been infrequent within this cohort. Third, treatment strategies were not randomly assigned. Therefore, the decision to initiate iHTN or modify antithrombotic therapy was likely influenced by clinicians' assessments of stroke severity or patient prognosis, introducing a potential indication bias. In particular, the antithrombotics change group likely represents a heterogeneous set of therapeutic decisions, and some patients in the conservative group may not have received active END management due to clinical contraindications. Likewise, patients in the iHTN group may have been selectively chosen based on the absence of significant cardiovascular comorbidities because vasopressors are generally avoided in conditions such as coronary artery disease. However, in our subgroup analyses, the beneficial association of iHTN was observed regardless of the presence of coronary heart disease or hypertension, suggesting that the influence of these comorbidities on the interpretation of our results is likely to be limited. Finally, as this was a cohort study, the treatment regimens, including the choice of agents, dosages, and target blood pressure levels, could not be standardized. Although most participating centers generally performed iHTN based on protocols from prior clinical trials,[11] variations across centers were still possible. Furthermore, we could not evaluate the absolute blood pressure values before and after treatment nor ascertain whether patients achieved the target blood pressure thresholds. Nevertheless, this study systematically evaluated real-world treatment patterns and outcomes following END in a large-scale, nationwide cohort, providing clinically relevant insights into current practice and potential therapeutic directions.

In conclusion, this study demonstrated that iHTN applied after the occurrence of progressive END in patients with noncardioembolic stroke was significantly associated with better neurological recovery and more favorable functional outcomes. Given the retrospective nature of the study, these results should be considered hypothesis-generating, and further validation through prospective randomized controlled trials is warranted.

ARTICLE INFORMATION

Received August 7, 2025; final revision received October 14, 2025; accepted October 20, 2025.

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Sources of Funding

This research was supported by funding from the Research of Korea Centers for Disease Control and Prevention (grant 2023-ER1006-00).

Disclosures

The authors report no conflicts. The authors confirm that this manuscript complies with all instructions to authors and confirm that authorship requirements have been met, and the final manuscript was approved by all authors. The authors confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. We followed the Strengthening the Reporting of Observational Studies in Epidemiology statement checklist for the report of an observational cohort study.

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