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Association between impaired brachial flow-mediated dilation and early neurological deterioration in acute ischemic stroke: a retrospective analysis

Sang Hee Ha[1], Bo Hye Yoon[1], Bon Gook Koo[1], Dong Hoon Shin[1], Yeong-Bae Lee[1*†] and Bum Joon Kim[2*†]

Abstract

Background Early neurological deterioration (END) occurs in individuals who had experienced acute ischemic stroke (AIS), impacting long-term functional outcomes. We aimed to investigate the association between endothelial function, measured via flow-mediated dilation (FMD), and END in patients with AIS.

Methods We retrospectively reviewed patients who had experienced AIS within 7 days of stroke onset and underwent FMD assessments during their hospitalization (%FMD = Peak diameter – baseline diameter)/baseline diameter x 100). END was defined as ≥ 2-point increase in the National Institutes of Health Stroke Scale total score or ≥ 1-point increase in the motor score within 72 h post-stroke. Through multivariate analysis, we examined factors associated with END and explored the relationship between FMD and END with considering stroke mechanisms.

Results Among 1,262 patients diagnosed with AIS, 184 (14.6%) experienced END. Those with END were on average older (69 ± 13 vs. 67 ± 13 years; $P = 0.033$), had a higher prevalence of stroke history (21.2 vs. 12.9%; $P = 0.003$), and lower FMD (5.0 ± 1.8 vs. 5.4 ± 2.2%; $P = 0.029$). Multivariate analysis revealed that a history of stroke (adjusted odds ratio [aOR] = 1.728; 95% confidence interval [CI] 1.159–2.578; $P = 0.007$) and low % were independently associated with END. Subgroup analysis revealed that low %FMD was significantly associated with END within the small vessel disease (SVD) category (aOR = 0.789; 95% CI 0.679–0.920; $P = 0.002$).

Conclusions Impaired FMD may be associated with END, particularly within the context of SVD.

Keywords Early neurological deterioration, Flow-mediated dilation, Acute ischemic stroke, Small vessel disease

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Introduction

Early neurological deterioration (END) refers to the worsening of symptoms after acute ischemic stroke (AIS), affecting 5–40% of patients and correlating with adverse outcomes [1]. Recognizing END predictors is vital for timely intervention to prevent acute-stage stroke progression [2]. END can stem from various mechanisms, including stroke progression, early recurrence, and cerebral edema [1]. Numerous studies have linked initial stroke severity, presence of diabetes mellitus, parent artery disease, high blood viscosity, and cerebral artery tortuosity to END [3, 4].

Additionally, endothelial dysfunction arising from vessel wall structural changes and cellular alterations has been associated with impaired cerebral blood flow regulation, contributing to reduced cerebral perfusion and stroke progression [5]. Moreover, endothelial dysfunction can increase the permeability of the blood-brain barrier, escalating the risk of brain edema [6]. Despite this, the connection between endothelial dysfunction and END in patients with AIS remains unexplored.

Brachial artery flow-mediated dilation (FMD), evaluated through high-resolution ultrasonography, serves as a widely utilized tool for assessing endothelial function [7]. Previous studies have demonstrated diminished FMD in patients who had experienced AIS compared to the normal population [8]. Moreover, patients who had experienced AIS with impaired FMD have demonstrated a correlation with unfavorable long-term functional outcomes [9]. This study aimed to identify factors associated with END in patients who had experienced AIS, with a specific emphasis on investigating the role of endothelial function as determined by FMD.

Materials and methods

Participants

We conducted a retrospective analysis involving patients who had experienced AIS (within 7 days of onset) and were admitted to Gil Medical Center between January 2018 and February 2023. Patients included in this study were confirmed to have AIS through diffusion-weighted imaging (DWI) and underwent FMD assessment during their hospitalization. Exclusions encompassed patients with: (1) DWI-negative transient ischemic attack; (2) initial imaging indicating intracranial hemorrhage; and (3) an inability to reliably undergo high-resolution ultrasonography due to lack of cooperation.

Approval for this study was granted by the local ethics committee of Gil Medical Center, South Korea (GAIRB number: 2023 – 119). Due to the retrospective nature of the study, the requirement for informed patient consent was waived. The study adhered to the relevant guidelines and regulations in all its methodologies.

Clinical data and END

Demographic data and risk factors were collected from medical records and the stroke registry database. Risk factors, comorbidities, and medication use at the time of stroke onset were assessed. Laboratory tests, including glycated hemoglobin (Hba1c), D-dimer, and lipid profiles (total cholesterol, low-density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride), were conducted on the day following admission after an appropriate fasting period. The cause of stroke was categorized according to the Trial of Org 10,172 in Acute Stroke Treatment classification (large artery atherosclerosis [LAA], small vessel disease [SVD], cardioembolism [CE], undetermined [UD], and other determined [OD]) [10].

Neurological deficits associated with stroke were evaluated using the National Institute of Health Stroke Scale (NIHSS) score upon admission by an experienced stroke neurologist. The NIHSS score was repetitively measured following admission, according to the center's protocol. END was defined as a ≥ 2-point increase in the NIHSS total score or ≥ 1-point score increase in the NIHSS motor score within the initial 72 h of admission, excluding non-neurological causes, such as medical condition deterioration or bodily injury [4, 11].

Measurement of flow-mediated dilation

During admission, endothelial function was assessed by measuring FMD of the brachial artery in response to hyperemia using a high-resolution B-mode ultrasound (Aplio 50 Toshiba SSA-700) with a 7.5-MHz linear-array transducer. FMD measurements were conducted when the patients were neurologically stable.

Participants were required to be well-rested and abstain from smoking, alcohol consumption, or caffeine intake for at least 6 h prior to the FMD measurements. A blood pressure cuff was placed on the forearm and occlusion was initiated by inflating the cuff to a minimum of 50 mmHg above the patient's systolic pressure for 5 min. Subsequently, the pressure was rapidly released to induce hyperemia in the hand and forearm, leading to reactive vasodilation in the brachial artery. This procedure was repeated twice within a 30-min interval. The percentage of FMD was calculated as 100 × [(Peak diameter – baseline diameter) / baseline diameter] [12, 13].

Statistical analysis

Baseline characteristics of patients with END and those without END were compared. Categorical variables were analyzed using the chi-square or Fisher's exact tests, whereas continuous variables were compared using the Student's t-tests or Mann–Whitney U-tests. Univariate and multivariate analyses were performed to explore factors associated with END. Age, sex (male), and variables

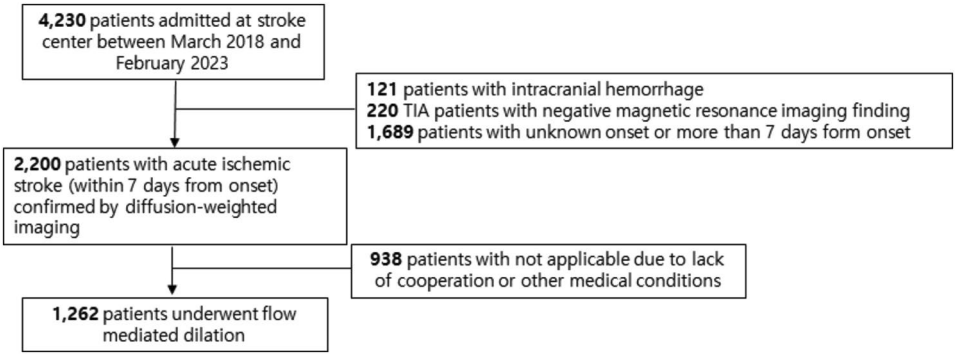

Fig. 1 Study flow chart

Table 1 Baseline characteristics of patients with and without early neurological deterioration

	END - (*n* = 1078)	END + (*n* = 184)	*P*-value
Age (years)	67 ± 13	69 ± 13	0.033
Sex, male	722 (67.0)	118 (64.1)	0.450
Hypertension	633 (58.7)	118 (64.1)	0.167
Diabetes mellitus	331 (30.7)	62 (33.7)	0.418
Hyperlipidemia	187 (17.3)	29 (15.8)	0.598
Atrial fibrillation	81 (7.5)	16 (8.7)	0.578
Smoking history	109 (10.1)	18 (9.8)	0.891
Previous stroke history	139 (12.9)	39 (21.2)	0.003
Previous antithrombotic	253 (23.5)	53 (28.8)	0.119
Previous statin use	249 (23.1)	54 (29.3)	0.067
Initial NIHSS score	2 (1–5)	3 (1–6)	0.228
IV tPA	120 (11.1)	20 (10.9)	0.917
EVT	71 (6.6)	11 (6.0)	0.757
TOAST classification			0.279
Large artery atherosclerosis	321 (29.8)	55 (29.9)	
Small vessel disease	369 (34.2)	76 (41.3)	
Cardioembolism	212 (19.7)	26 (14.1)	
Undetermined	30 (2.8)	5 (2.7)	
Other determined	146 (13.5)	22 (12.0)	
Lab findings			
Total cholesterol (mg/dL)	171 ± 96	167 ± 51	0.781
Triglyceride (mg/dL)	153 ± 202	146 ± 103	0.729
HDL-C (mg/dL)	42 ± 22	42 ± 12	0.731
LDL-C (mg/dL)	108 ± 56	107 ± 43	0.973
Hba1c (%)	6.6 ± 3.7	6.3 ± 1.3	0.728
D-Dimer (ng/mL)	582 ± 484	643 ± 535	0.462
FMD (%)	5.4 ± 2.2	5.0 ± 1.8	0.029

Results are presented as number (%), mean ± standard deviation (SD), or interquartile range (IQR)

END, early neurological deterioration; FMD, flow-mediated dilation; NIHSS: National Institutes of Health Stroke Scale; TOAST, Trial of Org 10,172 in Acute Stroke Treatment; IV tPA, intravenous tissue plasminogen activator; EVT, endovascular thrombectomy; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

with a significant association ($P < 0.1$) from the univariate analyses were incorporated into the multivariate logistic regression analysis. Subgroup analysis using logistic regression model was conducted for stroke mechanisms. All statistical analyses were conducted using IBM SPSS version 21.0 software (SPSS, Chicago, IL), and significance was set at $P < 0.05$.

Results

The study flow chart is depicted in Fig. 1. A total of 1,262 patients who had experienced AIS (within 7 days of onset) and underwent FMD were included in this study. The patients had a mean age of 67 ± 13 years, and 840 (66.5%) of them were men. The initial NIHSS score had a median of 2 (range 1–5). The median interval from symptom onset to admission was 1 day. FMD assessments were conducted within a median of 5 (range 3–6) days from the onset of symptoms, with an average %FMD of 5.4 ± 2.1%.

END and FMD

A total of 184 (14.6%) patients experienced END. Baseline characteristics of patients with and without END are presented in Table 1. No notable differences in vascular risk factors and laboratory results were observed between the two groups. In comparison to patients without END, those who experienced it were of older age (69 ± 13 vs. 67 ± 13 years; $P = 0.033$), had a higher prevalence of stroke history (21.2 vs. 12.9%; $P = 0.003$), and demonstrated lower %FMD (5.0 ± 1.8 vs. 5.4 ± 2.2%; $P = 0.029$).

Results from the univariate analysis indicated a significant association between a previous history of stroke and %FMD with the occurrence of END. The multivariate analysis further demonstrated that a history of stroke (adjusted odds ratio [aOR] = 1.728; 95% confidence interval [CI] 1.159–2.578; $P = 0.007$) and a low %FMD (aOR = 0.889; 95% CI 0.818–0.965; $P = 0.005$) were both independent factors associated with END (Table 2).

FMD according to stroke mechanisms

The demographics and risk factors based on the stroke mechanism are presented in Table 3. Notably, differences were observed in the proportion of patients who underwent reperfusion treatment. Distinct disparities were also

Table 2 Factors associated with early neurological deterioration

	Unadjusted univariate analysis		Adjusted multivariate analysis*	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)	1.011 (0.998–1.024)	0.088	-	
Sex, male	0.882 (0.636–1.222)	0.450	-	
Hypertension	1.257 (0.908–1.739)	0.168		
Diabetes mellitus	1.147 (0.823–1.598)	0.418		
Hyperlipidemia	0.891 (0.582–1.366)	0.598		
Atrial fibrillation	1.172 (0.669–2.053)	0.578		
Smoking history	0.964 (0.570–1.630)	0.891		
Previous stroke history	1.817 (1.223–2.699)	0.003	1.728 (1.159–2.578)	0.007
Previous thrombotic	1.319 (0.931–1.870)	0.119		
Previous statin	1.383 (0.977–1.958)	0.067	-	
Initial NIHSS score	1.037 (0.998–1.077)	0.062	1.034 (0.995–1.076)	0.089
IV tPA	0.974 (0.590–1.608)	0.917		
EVT	0.902 (0.468–1.737)	0.757		
TOAST classification				
Large artery atherosclerosis	1 (Reference)			
Small vessel disease	1.202 (0.824–1.754)	0.340		
Cardioembolism	0.716 (0.435–1.177)	0.188		
Undetermined	0.973 (0.362–2.615)	0.956		
Other determined	0.879 (0.517–1.497)	0.636		
Lab findings				
Total cholesterol (mg/dL)	0.999 (0.997–1.002)	0.601		
Triglyceride (mg/dL)	1.000 (0.999–1.001)	0.701		
HDL-C (mg/dL)	0.998 (0.989–1.007)	0.693		
LDL-C (mg/dL)	1.000 (0.997–1.003)	0.819		
Hba1c (%)	0.940 (0.842–1.051)	0.278		
D-Dimer (ng/mL)	1.000 (1.000–1.001)	0.465		
FMD (%)	0.888 (0.818–0.965)	0.005	0.889 (0.818–0.965)	0.005

Results are presented as odds ratios (OR) and 95% confidence interval (CI)

END, early neurological deterioration; FMD, flow-mediated dilation; NIHSS: National Institutes of Health Stroke Scale; TOAST, Trial of Org 10,172 in Acute Stroke Treatment; IV tPA, tissue plasminogen activator; EVT, endovascular thrombectomy; LDL-C, low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol

* Multivariate logistic regression adjusted for age, sex, initial NIHSS score, previous statin, previous stroke history, and FMD (%)

observed in the lipid profile, HbA1c levels, and D-dimer values corresponding to the stroke mechanisms. Analysis of FMD values revealed lower measurements in individuals with SVD at 5.1 ± 1.9, followed by LAA at 5.4 ± 2.1, OD at 5.4 ± 2.0, CE at 5.7 ± 2.5, and UD at 5.8 ± 2.3.

Subgroup analysis for stroke mechanisms demonstrated that a reduced %FMD was significantly associated with END in cases of SVD mechanism (aOR = 0.789; 95% CI 0.679–0.920; $P = 0.002$), whereas no association was observed among patients with other stroke mechanisms (Fig. 2).

Discussion

In the present study, we identified a history of stroke and impaired FMD as independent factors associated with END in patients diagnosed with AIS. Subgroup analysis categorized by stroke mechanisms revealed a notable correlation between impaired FMD and the occurrence of END, specifically among patients affected by SVD.

Endothelial dysfunction is frequently accompanied by an imbalance between nitric oxide (NO) and reactive oxygen species (ROS), characterized by reduced NO and elevated ROS levels [14]. This imbalance contributes to the impairment of endothelium-dependent vasodilation [15]. The decrease in NO production leads to compromised regulation of cerebral blood flow, rendering it sensitive to elevated shear forces and resulting in hypoperfusion. Consequently, the microcirculation regulation is disrupted, culminating in cerebral hypoperfusion [16]. Elevated ROS levels triggers uncontrolled inflammatory signaling, contributing to the progression of cardiovascular conditions, such as atherosclerosis [16]. Additionally, these activate matrix metalloproteinase-9, resulting in the breakdown of the brain-blood barrier and increasing susceptibility to brain edema [17, 18]. Collectively, these mechanisms partially elucidate the association between FMD and END in patients diagnosed with AIS.

Table 3 Baseline characteristics of the participants according to the stroke mechanisms

	LAA (*n* = 376)	SVD (*n* = 445)	CE (*n* = 238)	UD (*n* = 35)	OD (*n* = 168)	*p*
Age (years)	67 ± 13	67 ± 11	70 ± 12	55 ± 16	68 ± 14	< 0.001
Sex, male	276 (73.4)	280 (62.9)	144 (60.5)	21 (60.0)	119 (70.8)	0.002
Hypertension	240 (63.8)	261 (58.7)	129 (54.2)	15 (42.9)	106 (63.1)	0.029
Diabetes mellitus	132 (35.1)	156 (35.1)	45 (18.9)	5 (14.3)	55 (32.7)	< 0.001
Hyperlipidemia	59 (15.7)	88 (19.8)	34 (14.3)	8 (22.9)	27 (16.1)	0.283
Atrial fibrillation	5 (1.3)	2 (0.4)	74 (31.1)	0	16 (9.5)	< 0.001
Smoking history	48 (12.8)	35 (7.9)	23 (9.7)	4 (11.4)	17 (10.1)	0.238
Previous stroke history	52 (13.8)	64 (14.4)	33 (13.9)	2 (5.7)	27 (16.1)	0.621
Previous antithrombotic	83 (22.1)	103 (23.1)	81 (34.0)	3 (8.6)	36 (21.4)	0.001
Previous statin use	85 (22.6)	114 (25.6)	55 (23.1)	6 (17.1)	43 (25.6)	0.685
Initial NIHSS score						
IV tPA	47 (12.5)	22 (4.9)	54 (22.7)	2 (5.7)	15 (8.9)	< 0.001
EVT	31 (8.2)	0	39 (16.4)	0	12 (7.1)	< 0.001
Lab findings						
Total cholesterol (mg/dL)	171 ± 125	178 ± 87	162 ± 45	174 ± 86	161 ± 50	< 0.001
Triglyceride (mg/dL)	146 ± 95	172 ± 286	128 ± 141	149 ± 72	141 ± 84	< 0.001
HDL-C (mg/dL)	39 ± 10	43 ± 25	43 ± 13	37 ± 10	43 ± 32	< 0.001
LDL-C (mg/dL)	108 ± 41	114 ± 70	101 ± 41	110 ± 56	101 ± 40	0.010
Hba1c (%)	6.5 ± 1.5	6.5 ± 1.5	6.4 ± 6.3	5.9 ± 4.5	6.5 ± 3.4	< 0.001
D-Dimer (ng/mL)	630 ± 471	475 ± 461	680 ± 545	116 ± 162	657 ± 457	0.002
FMD (%)	5.4 ± 2.1	5.1 ± 1.9	5.7 ± 2.5	5.8 ± 2.3	5.4 ± 2.0	0.002
END	55 (14.6)	76 (17.1)	26 (10.9)	5 (14.3)	22 (13.1)	0.279

Results are presented as number (%), mean ± standard deviation (SD), or interquartile range (IQR)

LAA, large artery atherosclerosis; SVD, small vessel disease; CE, cardiac embolism; UD, undetermined; OD, other determined; END, Early neurological deterioration; FMD, Flow mediated dilation; NIHSS: National Institutes of Health Stroke Scale; TOAST, Trial of Org 10,172 in Acute Stroke Treatment; IV tPA, intravenous tissue plasminogen activator; EVT, endovascular thrombectomy; LDL-C, low-density lipoprotein cholesterol; HDL, High-density lipoprotein cholesterol

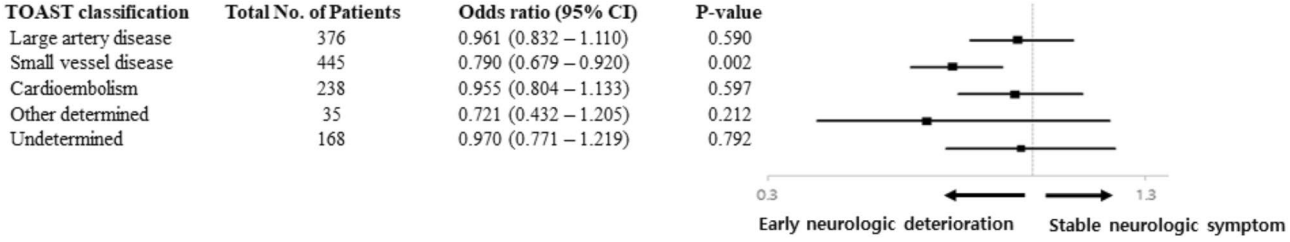

Fig. 2 Subgroup analysis. Logistic regression analysis of the association between FMD and END according to the stroke subtype. FMD, flow-mediated dilation; END, early neurological deterioration

Notably, individuals with compromised %FMD exhibited a heightened susceptibility to END, particularly within the subset of patients with an SVD mechanism. Prior investigations have demonstrated that serum markers indicating endothelial activation are most elevated in patients affected by SVD among various stroke subtypes [19]. This finding aligns with our current study's findings, which indicate that FMD was most significantly impaired in patients with SVD. Although concerns might arise regarding whether assessing endothelial function through the brachial artery sufficiently captures endothelial dysfunction within cerebral perforators, several studies have provided evidence supporting the notion that the systemically circulating markers of endothelial activation in patients with SVD align with the hypothesis that cerebral SVD is indeed a component of systemic vasculopathy [20].

The majority of END cases observed within the context of SVD stem from hypoperfusion through the perforators, contributing to stroke progression [21]. Endothelial dysfunction, as indicated by diminished FMD, may explain the association between reduced FMD and the occurrence of END in patients with SVD. This phenomenon could serve as a viable therapeutic target during the acute phase of stroke to prevent END [22]. Additionally, these findings align with those of previous studies suggesting that improving endothelial function is a prospective strategy for reducing END occurrence in patients diagnosed with AIS [22–24]. FMD has the potential to serve as a predictive indicator for END in patients who

had experienced AIS, offering a promising avenue for its utilization as a biomarker to assess therapeutic efficacy.

This study had several limitations. First, the study cohort consisted of a limited number of stroke cases and was conducted solely within a single center, potentially impacting the generalizability of the findings. Second, we postulated various potential implications of endothelial dysfunction on END, with a particular emphasis on hemodynamic factors. Unfortunately, the study's design prevented us from directly assessing these factors, thereby limiting our ability to comprehensively evaluate their contributions to the observed outcomes. Third, we excluded patients with severe strokes or those unable to cooperate due to other medical conditions. This may have led to a study population with relatively mild neurological severity, potentially limiting the generalizability of our findings. Finally, although the original intention was to perform FMD assessments before the occurrence of END to identify predictors, most patients underwent these assessments at a median of 5 days post-admission. Only 21 patients (11.4%) received FMD assessments prior to experiencing END. Nevertheless, our analysis revealed no significant differences in FMD percentage values between patients assessed before END (4.86 ± 2.03) and those assessed after (4.96 ± 1.82). This outcome suggests that FMD percentage values may not significantly vary during the acute phase of ischemic stroke. Additionally, previous research supports that endothelial function, as measured by FMD, exhibits minimal fluctuation during this critical period [25].

Recognizing the inherent limitations of our study, our findings still indicate a potential correlation between reduced %FMD and END, with a more pronounced association evident in instances of SVD. Considering that END in patients with AIS can significantly contribute to increased rates of functional disability, early identification of individuals prone to progression is crucial. By identifying these individuals early, their clinical and therapeutic strategies could potentially be enhanced, ultimately improving patient outcomes.

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None.

Author contributions
Sang Hee Ha contributed to the study concept, study design, data collection, data interpretation, and drafting and revising the manuscript.Bo Hye Yoon contributed to the data interpretation and revising the manuscript.Bon Gook Koo contributed to the data interpretation and revising the manuscript.Dong Hoon Shin contributed to the data interpretation and revising the manuscript. Yeong-Bae Lee and Bum Joon Kim contributed to the study concept, study design, data interpretation, and drafting and revising the manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study protocol was reviewed and approved by from the Institutional Review Board of Gil medical center, approval number (GAIRB number: 2023 – 119) Informed consent was waived because of the retrospective design by the ethic committee of Gil Medical Center. All experiments were performed in accordance with relevant guidelines and regulations (such as the Declaration of Helsinki).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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