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High-on-Aspirin Platelet Reactivity Differs Between Recurrent Ischemic Stroke Associated With Extracranial and Intracranial Atherosclerosis

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Background and Purpose Ischemic stroke recurs despite the use of antiplatelet agents. Various mechanisms are involved in recurrence due to intracranial atherosclerosis (ICAS) and extracranial atherosclerosis (ECAS). High-on-aspirin platelet reactivity (HAPR) may differ between recurrent stroke due to ICAS and ECAS.

Methods Patients with recurrent ischemic stroke as a result of large-artery atherosclerosis despite taking aspirin were enrolled consecutively. Ischemic stroke was classified as stroke due to ICAS or ECAS according to the location of the culprit stenosis. An aspirin reaction units (ARU) value of >550 IU was defined as HAPR. HAPR and its associated factors were compared between the two groups and also considering the mechanism of stroke.

Results Among the 190 patients with recurrent stroke (111 with ICAS and 79 with ECAS), 36 (18.3%) showed HAPR. The ARU value was higher in the ECAS than the ICAS group (492±83 vs. 465±78, mean±standard deviation; p=0.028), as was the proportion of patients with HAPR (27.8% vs. 12.6%, p=0.008). Being male and having stroke due to ECAS (reference = stroke due to ICAS: odds ratio=5.760; 95% confidence interval=2.154−15.403; p<0.001) was independently associated with HAPR. The ARU value differed according to the stroke mechanism, and was highest in those with artery-to-artery embolism. Artery-to-artery embolism was independently associated with HAPR in both the ICAS and ECAS groups.

Conclusions Recurrent stroke due to ECAS was more strongly associated with HAPR and insufficient antiplatelet inhibition than was that due to ICAS. Artery-to-artery embolism was associated with HAPR in recurrent ischemic stroke as a result of ICAS or ECAS.

Keywords recurrent stroke; aspirin resistance; atherosclerosis; embolism; stroke mechanism.

INTRODUCTION

The optimal strategy for preventing secondary stroke depends on the mechanism of stroke. For patients with large-artery atherosclerosis (LAA), platelet activation in the stenosis area with a distal embolization has been found to be the main mechanism causing ischemic stroke.[1] Therefore, antiplatelet treatment has been regarded as the standard medical treatment for secondary prevention.[2] A considerable proportion of patients experience recurrent stroke despite receiving appropriate antiplatelet treatment. Recurrent stroke may be caused by poor compliance with medication, other uncontrolled risk factors, stroke mechanisms that are less dependent on platelet activation (i.e., cardioembolism or Moyamoya disease), or insufficient platelet inhibition due to high-on-treatment platelet reactivity (HPR).[3-5] Previous studies have found HPR to result in a significantly higher risk of recurrent isch-

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emic stroke or transient ischemic attack, and also embolic infarction in various conditions.[6,7]

LAA can be found in intracranial and extracranial cerebral arteries. Intracranial atherosclerosis (ICAS) and extracranial atherosclerosis (ECAS) share common risk factors, but they have different impacts. Various mechanisms have been found to be involved in ischemic stroke as a result of LAA, with the detailed mechanism involved in stroke differing between ICAS and ECAS: most cases of stroke in those with ECAS were artery-to-artery embolisms, whereas the mechanisms involved in ICAS were more variable.[8] Therefore, we hypothesized that the relative importance of platelet activation differs between recurrent stroke patients associated with ICAS and ECAS. To verify this, HPR was measured and compared between recurrent ischemic stroke patients associated with ICAS and ECAS. Factors associated with HPR were also investigated, and the detailed stroke mechanism was further considered.

METHODS

Patients

Ischemic stroke patients admitted to a tertiary stroke center within 7 days of stroke onset were prospectively included in the study sample. Patients were consecutively enrolled in the study between January 2010 and December 2017 if they had been receiving aspirin or aspirin plus clopidogrel treatment, had an ischemic lesion confirmed by diffusion-weighted imaging (DWI), had significant stenosis (>50%) or occlusion in the corresponding artery that resulted in the index stroke, and were classified as LAA according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification.[1] Patients with other sources of emboli (i.e., atrial fibrillation, valvular heart disease, or active coagulopathy) or other determined cause (e.g., Moyamoya disease or dissection) were excluded. Patients without adequate magnetic resonance image (MRI) data or those who were not taking a prescribed antiplatelet agent (aspirin or aspirin plus clopidogrel) regularly were also excluded. Clinical data including demographics, vascular risk factors, and concomitant medication at the onset of stroke were obtained from the registry database. The study design was approved by the ethical committee of Kyung Hee University Hospital (IRB No. KHUH 2017-04-062); informed consent was not required due to the retrospective design of the study.

Imaging analysis and location of atherosclerosis

MRI was performed on the day of admission, which included DWI, fluid-attenuated inversion recovery and gradient echo sequences, time-of-flight magnetic resonance angiography (MRA), and contrast-enhanced MRA. The presence of ischemic stroke and the lesion pattern were analyzed based on the DWI data.

The location of atherosclerosis was determined from the MRA data. Symptomatic stenosis of the common carotid artery, proximal internal carotid artery (ICA), or vertebral artery (VA) was considered as extracranial artery stenosis. Intracranial artery stenosis was defined as stenosis of the distal ICA, anterior cerebral artery, middle cerebral artery (MCA), posterior cerebral artery, distal VA, or basilar artery.

The detailed mechanism of stroke was determined by the lesion pattern in DWI as follows: artery-to-artery embolism infarction (single or scattered lesions at the cortex with or without border-zone infarction), local branch occlusion infarction (striatocapsular infarct or a perforating vessel infarct of the MCA with significant stenosis of >50% or occlusion at the MCA, where the perforator may originate, a single lesion of any size with subcortical infarction considered as a local branch occlusion), in situ thrombosis (MCA occlusion with a territorial infarction), or hemodynamic infarction (border-zone infarction with evidence of blood-pressure lowering or dehydration). In addition, a combined mechanism was defined as a scattered cortical infarction plus an additional infarction in the perforator territory.[9]

Two experienced neurologists (K.C. Noh and B.J. Kim) evaluated the mechanism of stroke independently, and any discrepancies in the final location of atherosclerosis and stroke mechanism were resolved at a consensus meeting.

High-on-treatment platelet reactivity

The patient history and medical records were reviewed to identify any previous use of an antiplatelet agent. If an antiplatelet agent had been prescribed at another center, the center was called for confirmation. The patient or their caregiver was required to confirm that the antiplatelet agent had been taken regularly as prescribed; the patient was excluded from the analysis if this could not be confirmed.

The extent of platelet inhibition by antiplatelet agents was measured using the VerifyNow Aspirin and VerifyNow P2Y12 devices (Accumetrics, San Diego, CA, USA). On the day of admission, the blood samples were transferred to dedicated cartridges containing arachidonic acid (VerifyNow Aspirin) or fibrinogen-coated beads, thrombin-receptor-activating peptide, adenosine diphosphate, and prostaglandin E1 (VerifyNow P2Y12). Changes in the light transmission induced by platelet aggregation were measured. Results were expressed as aspirin reaction units (ARU), P2Y12 reaction units (PRU), and percentage of platelet inhibition (%PI). The usual criterion of ARU >550 was used to define high-on-aspirin platelet reactivity (HAPR), while that of %PI <20 was used to de-

fine high-on-clopidogrel platelet reactivity (HCPR).[10,11]

Statistical analysis

The characteristics of recurrent ischemic stroke were compared between patients in the symptomatic ICAS and ECAS groups, as were the resistance to antiplatelet agents and the exact values of ARU, PRU, and %PI. The chi-square test, Fisher's exact test, and Student's t-test were used as appropriate. Factors associated with HAPR were investigated using univariable and multivariable analyses. Factors with a potential association (p<0.15) in the univariable analysis were included in the multivariable model.

ARU values in recurrent ischemic stroke with different stroke mechanisms were further compared separately in ECAS and ICAS patients. ANOVA was used to compare ARU values among different stroke mechanisms in ICAS and ECAS. Factors associated with HAPR were also investigated in each group. The stroke mechanism was dichotomized into artery-to-artery embolism and other mechanisms. All statistical analyses were performed using SPSS for Windows (version 17.0, SPSS, Chicago, IL, USA), and a two-sided p value <0.05 was considered statistically significant.

RESULTS

During the study period, 5,261 patients were registered in the database, with a previous history of stroke (recurrent stroke) present in 786 of them. Treatment with aspirin or aspirin plus clopidogrel was being applied at the time of recurrence in 613 patients, and 205 of these patients were categorized as having LAA. Finally, 190 patients with ARU data were enrolled in the study. Clopidogrel was administered in addition to aspirin in 59 patients, and the PRU value was measured in 54 patients.

The study participants were aged 71±9 years (mean±standard deviation), and 117 (61.6%) were male, 171 (90.0%) had hypertension, 91 (47.9%) had diabetes, 133 (70.0%) had hyperlipidemia, and 84 (44.2%) were current smokers. HAPR was identified in 36 (18.3%) of 190 patients and HCPR in 19 (35.2%) of 54 patients. The location of atherosclerosis was intracranial in 111 (58.4%) patients and extracranial in 79 (41.6%).

Location of atherosclerosis and HAPR

The characteristics of patients with symptomatic ICAS and ECAS are presented in Table 1. Patients were older in the ICAS than the ECAS group (69.7±9.5 vs. 73.5±7.6 years, p=0.004), but there were no other intergroup differences in demographics or risk factors. Most of the ECAS patients (n=58, 73.4%) had artery-to-artery embolism, whereas the mechanism of stroke in ICAS patients was more diverse, including 20 (18.0%) patients with local branch occlusion and 24 (21.6%) with a combined mechanism.

Table 1. Characteristics of recurrent ischemic stroke patients with ICAS and ECAS

	ICAS (n=111)	ECAS (n=79)	p
Age (yr)	69.7±9.5	73.5±7.6	0.004
Sex, male	61 (55.0)	53 (67.1)	0.092
Hypertension	98 (88.3)	73 (92.4)	0.351
Diabetes	55 (49.5)	36 (45.6)	0.588
Hyperlipidemia	76 (68.5)	57 (72.2)	0.585
Current smoker	49 (44.1)	35 (44.3)	0.929
Detailed mechanism			<0.001
Artery-to-artery embolism	51 (45.9)	58 (73.4)	
Local branch occlusion	20 (18.0)	0 (0.0)	
In situ thrombosis	9 (8.1)	10 (12.7)	
Hemodynamic infarction	7 (6.3)	8 (10.1)	
Combined	24 (21.6)	3 (3.8)	
Additional clopidogrel	29 (26.1)	30 (38.0)	0.082
Statin	51 (45.9)	30 (38.0)	0.228
Aspirin reaction units (IU)	465±78	492±83	0.028
Aspirin resistance	14 (12.6)	22 (27.8)	0.008
P2Y12 reaction units (IU)*	271±78	254±73	0.393
Platelet inhibition (%)*	13±17	15±16	0.707
Clopidogrel resistance*	17 (63.0)	18 (66.7)	0.776

Data are mean±standard-deviation or number (%) values.
*Among patients who received clopidogrel at stroke onset and the P2Y12 VerifyNow test.
ECAS, extracranial atherosclerosis; ICAS, intracranial atherosclerosis; IU, international units.

The ARU value was significantly higher in patients with recurrent ischemic stroke due to ECAS than in those with ICAS (492±83 vs. 465±78, p=0.028). The proportion of patients with HAPR was higher in the ECAS group than the ICAS group (27.8% vs. 12.6%, respectively; p=0.008), whereas HCPR did not differ between the two groups.

Among recurrent ischemic stroke patients with LAA, HAPR was significantly associated with stroke due to ECAS (reference=stroke due to ICAS: odds ratio [OR]=2.674, 95% confidence interval [CI]=1.269−5.637, p=0.010). From the multivariable analysis, being male (OR=2.607, 95% CI=1.142−5.953, p=0.023) and having stroke due to ECAS (reference=stroke due to ICAS: OR=5.760, 95% CI=2.154−15.403, p<0.001) were independently associated with HAPR (Table 2).

Mechanism of stroke and HAPR

Among patients with recurrent stroke due to ECAS, the ARU value was highest in those with artery-to-artery embolism (509±82, n=58), followed by in situ thrombosis (470±

89, *n*=10), combined mechanism (429±52, *n*=3), and hemodynamic infarction (419±24, *n*=8); the difference of ARU value of stroke mechanisms was statistically significant (*p*=0.010; Fig. 1). Factors associated with HAPR among ECAS patients were the use of additional clopidogrel (OR=0.265, 95% CI=0.080–0.882, *p*=0.030) and artery-to-artery embolism (reference=other mechanisms: OR=5.000, 95% CI=1.057–23.661, *p*=0.042). The multivariable analysis indicated that artery-to-artery embolism (reference=other mechanisms: OR=5.174, 95% CI=1.036–25.844, *p*=0.045) was the

Table 2. Factors associated with high-on-aspirin platelet reactivity

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.042 (0.997–1.089)	0.065		
Male sex	2.070 (0.994–4.309)	0.052	2.607 (1.142–5.953)	0.023
Hypertension	0.620 (0.208–1.849)	0.391		
Diabetes	1.680 (0.806–3.502)	0.166		
Hyperlipidemia	0.708 (0.329–1.520)	0.376		
Current smoker	0.587 (0.273–1.264)	0.173		
Additional use of clopidogrel	0.473 (0.194–1.153)	0.100		
Statin	0.698 (0.329–1.480)	0.349		
ECAS (vs. ICAS)	2.674 (1.269–5.637)	0.010	5.760 (2.154–15.403)	<0.001

Factors included in the multivariable analysis: age, male sex, initial National Institutes of Health Stroke Scale score, additional use of clopidogrel, and ECAS.
CI, confidence interval; ECAS, extracranial atherosclerosis; ICAS, intracranial atherosclerosis; OR, odds ratio.

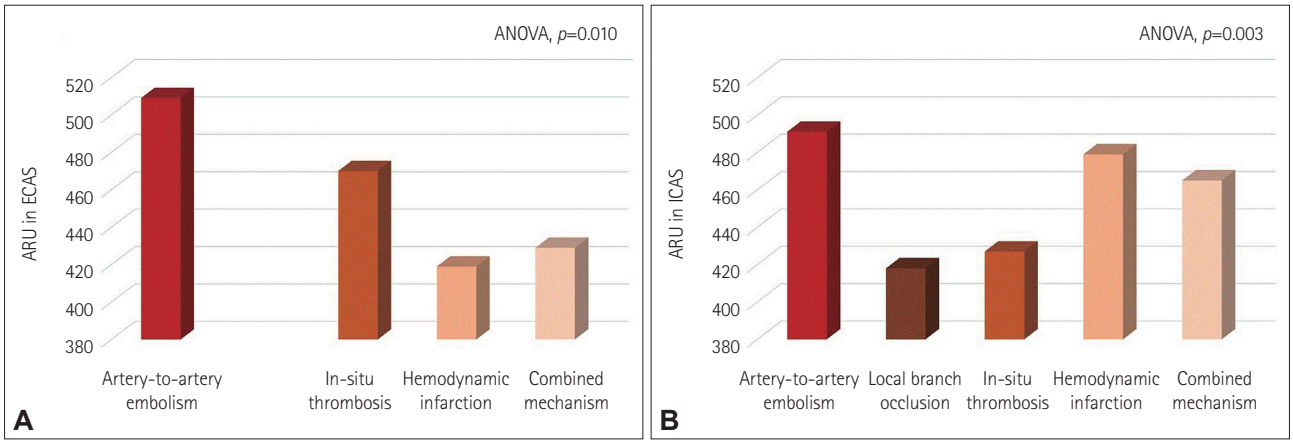

Fig. 1. Comparison of aspirin reaction units (ARU) values between different stroke mechanisms based on lesion pattern among patients with stroke due to extracranial atherosclerosis (ECAS) (A) and intracranial atherosclerosis (ICAS) (B).

Table 3. Factors associated with high-on-aspirin platelet reactivity among extracranial atherosclerosis patients

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age	1.039 (0.971–1.111)	0.268		
Male sex	2.135 (0.771–5.915)	0.144		
Hypertension	0.352 (0.065–1.895)	0.224		
Diabetes	1.280 (0.478–3.431)	0.624		
Hyperlipidemia	0.570 (0.198–1.640)	0.297		
Current smoker	0.635 (0.231–1.747)	0.379		
Additional use of clopidogrel	0.265 (0.080–0.882)	0.030		
Statin	0.690 (0.243–1.955)	0.485		
Artery-to-artery embolism (vs. other mechanisms)	5.000 (1.057–23.661)	0.042	5.174 (1.036–25.844)	0.045

Factors included in the multivariable analysis: male sex, initial National Institutes of Health Stroke Scale score, additional use of clopidogrel, and artery-to-artery embolism.

Table 4. Factors associated with high-on-aspirin platelet reactivity among intracranial atherosclerosis patients

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age	1.029 (0.967–1.095)	0.370		
Male sex	2.795 (0.870–8.975)	0.084		
Hypertension	0.767 (0.151–3.890)	0.749		
Diabetes	2.889 (0.848–9.847)	0.090		
Hyperlipidemia	0.806 (0.249–2.610)	0.719		
Current smoker	0.504 (0.145–1.748)	0.280		
Additional use of clopidogrel	0.745 (0.192–2.882)	0.670		
Statin	0.833 (0.269–2.586)	0.752		
Artery-to-artery embolism (vs. other mechanisms)	3.415 (1.001–11.653)	0.050	4.305 (1.166–15.894)	0.028

Factors included in the multivariable analysis: male sex, diabetes, initial National Institutes of Health Stroke Scale score, and artery-to-artery embolism.

only independent factor associated with HAPR in patients with recurrent ischemic stroke due to ECAS (Table 3).

Also among patients with recurrent stroke due to ICAS, the ARU value was highest in those with artery-to-artery embolism (491±79, *n*=51), followed by hemodynamic infarction (479±73, *n*=7), combined mechanism (465±78, *n*=24), in situ thrombosis (427±57, *n*=9), and local branch occlusion (418±73, *n*=20). The ARU value among ICAS patients with different mechanisms showed significant statistical difference (*p*=0.003; Fig. 1). Artery-to-artery embolism (reference=other mechanisms: OR=3.415, 95% CI=1.001–11.653, *p*=0.050) was associated with HAPR among patients with recurrent stroke due to ICAS. The multivariable analysis indicated that artery-to-artery embolism (OR=4.305, 95% CI=1.166–15.894, *p*=0.028) was independently associated with HAPR in patients with recurrent ischemic stroke due to ICAS (Table 4).

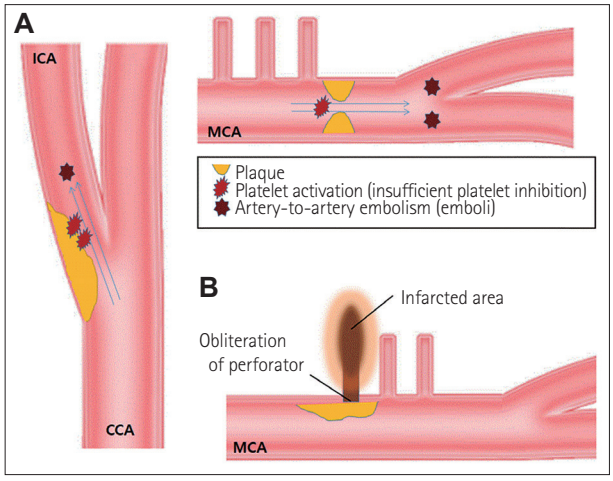

Fig. 2. Schematic drawings of recurrent stroke mechanism and biochemical aspirin resistance: insufficient platelet inhibition and artery-to-artery embolism (A) and obliteration of a perforator and local branch occlusion (B). CCA, common carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery.

DISCUSSION

In this sample of recurrent ischemic stroke patients with LAA, the ARU value was higher and HAPR was observed more frequently in patients with ECAS than in those with ICAS. Recurrent stroke due to ECAS was independently associated with the presence of HAPR. Regarding the mechanism of stroke, patients with artery-to-artery embolism showed higher ARU values than did those with other mechanisms, and this was independently associated with HAPR in both the ICAS and ECAS groups.

The main mechanism of ischemic stroke in patients with symptomatic ECAS is artery-to-artery embolism.[8] A plaque rupturing from areas of the carotid artery experiencing high shear stress may lead to arterial embolism and ischemic stroke.[12] High shear stress is known to induce angiogenesis within the plaque, which leads to the formation of vulnerable plaques that are prone to rupture.[13] High shear stress itself also leads to shear-induced platelet aggregation that is insensitive to aspirin,[14] and aspirin was found to insufficiently inhibit platelets under high shear stress conditions in an in vitro study.[15] In a study of patients with symptomatic carotid artery disease, more microembolic signals were observed in patients with HAPR.[16] Since artery-to-artery embolism is the main mechanism of stroke in patients with symptomatic ECAS, insufficient platelet inhibition as a result of HAPR may play an important role in stroke recurrence.

The mechanism of stroke is much more diverse in patients with symptomatic ICAS. Artery-to-artery embolism still remains the main mechanism of stroke, and is more common in those with enhanced plaques in high-resolution MRI.[17] Such plaques are also regarded as vulnerable plaques that are rich in inflammatory molecules and prone to rupture, with the potential to cause early stroke recurrence.[18] Vascular inflammation has been suggested as one of the potential

mechanisms of HAPR.[10] The current study found that ARU values were highest in patients with artery-to-artery embolism among those with recurrent stroke due to ICAS, and that artery-to-artery embolism was independently associated with HAPR. Platelet activation may still be important in ICAS patients with recurrent stroke due to artery-to-artery embolism (Fig. 2A). However, the ARU values were lowest in those with local branch occlusion. Platelet activation might be less important since local branch occlusion is caused by the obliteration of the orifice of perforators by atherosclerosis (Fig. 2B).[19]

HAPR is reportedly observed in 10%−30% of patients with recurrent ischemic stroke receiving aspirin therapy, and has been associated with both the long- and short-term recurrence of ischemic stroke.[20] Adding a second antiplatelet agent after recurrent stroke despite receiving aspirin therapy has previously been found to be more effective in preventing further stroke events.[21] Adding clopidogrel was associated with reducing HAPR changes in patients with recurrent stroke due to ECAS. Adding a potent antiplatelet agent to aspirin therapy may reduce the insufficiency of platelet inhibition in patients with recurrent ischemic stroke due to ECAS.[22] In contrast, focusing on decreasing the atherosclerotic burden might be more important when treating patients with local branch occlusion due to ICAS.[23]

The first limitation of the current study was its retrospective design. Second, the study was conducted in a single center, which may limit the generalizability of the results. However, restricting the study to a single center provided the advantage that the ARU values in patients with a previous stroke history and taking aspirin could be measured throughout the study period in accordance with the center protocol. Third, the ARU value (a serologic biomarker) was used to investigate differences in the role of insufficient platelet inhibition among different stroke mechanisms associated with LAA. Since biomarkers are influenced by various factors such as hematologic conditions and concurrent infections, and the cutoff values are arbitrary, using a prospective design with a clinical outcome might have strengthened our hypothesis. Fourth, determining the etiology of stroke solely based on the lesion pattern in DWI can be challenging and is not definitive, but this approach is still widespread in clinical practice. Fifth, only a small number of patients experienced recurrent stroke following combined treatment with clopidogrel, and so the effect of clopidogrel resistance on different mechanisms of stroke could not be evaluated. Since clopidogrel resistance is influenced by genetic factors and concomitant medication, a well-designed prospective study involving a larger number of patients with recurrent stroke and taking clopidogrel may be required to clarify this issue. Finally, the mechanism of stroke was based on the recurrent stroke, and little information was available on the mechanism of prior stroke.

Notwithstanding these limitations, the current study shows that ischemic recurrent stroke occurring in the presence of aspirin therapy due to ECAS is associated with HAPR and insufficient platelet inhibition. The artery-to-artery embolism in LAA is associated with aspirin resistance and insufficient platelet inhibition, whereas platelet inhibition plays only a minor role in recurrent ischemic stroke due to local branch occlusion.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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